

**Development of Three Reaction Methodologies En Route to
Nitrogen Containing Heterocycles: a Diels–Alder/Schmidt, a Diels–
Alder/Acylation and a Catalytic Intramolecular Schmidt**

by

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Thesis committee

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this is the approved version of the following dissertation:

**Development of Three Reaction Methodologies En Route to Nitrogen
Containing Heterocycles: a Diels–Alder/Schmidt, a Diels–
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Abstract

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Department of Medicinal Chemistry, September 2009

University of Kansas

This thesis describes three new advances in the synthesis of nitrogen containing heterocycles. The first two chapters discuss the development of two different domino reaction sequences: a Diels–Alder/Schmidt and a Diels–Alder/acylation sequence. The third chapter then explores the development of a first-generation catalytic Schmidt reaction.

The domino Diels–Alder/Schmidt reaction exploits two modes of reactivity. The first method reacted the azide and ketone groups on separate molecules, since it had been established in previous work that intermolecular Schmidt reactions only occur under special circumstances. An initial Diels–Alder reaction followed by a subsequent intramolecular Schmidt reaction was observed. This mode of reactivity was used to synthesize several interesting alkaloid-like skeleta. The second method was to deactivate the ketone for intramolecular azide attack by converting it into an enone. The Schmidt reaction did not occur until the enone had participated in a Diels–Alder reaction, thus providing control of this domino reaction. The enone deactivation method was used to form *trans*-hexahydroindoles and homopyrrolo[2.1-*j*]quinolin-5-ones.

Also described herein is the development of a one-pot domino Diels–Alder/acylation strategy to form octahydroisoquinolinone scaffolds. The reaction exploits the reactivity of maleic anhydride toward variously substituted amino dienes

providing exclusively the endo product. This work resulted in a scalable synthetic sequence tolerant of a wide range of substitution. The products also contain olefin and carboxylic acid groups suitable for further functionalization.

Finally, studies towards the development of a catalytic, intramolecular Schmidt reaction of ketones and azides are described. Building on an initial positive result employing 50 mol% Sc(OTf)₃ in water, conditions were explored for promoting this reaction sequence. Reaction surveys exploring solvents, Lewis and protic acids, and reaction conditions were completed. These studies led to the identification of conditions using a phase transfer catalyst (*n*-Bu₄NOH or *n*-Bu₄NCl) and microwave irradiation that accelerate the reaction with a broader range of substrates.

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throughout the years. I must also thank Michal Szostak for his keen chemical insight, friendship, encouragement and advice during our years in lab together. Good luck in all of your future endeavors, I expect great things. Dr. Erik Fenster, thank you for always being up for “talking chemistry,” giving advice and pushing me to think critically. Thanks also to Dr. Scott Grecian, for providing chemistry insight and the back-up I needed when things went south in Smissman. Finally, I must thank our honorary group member, Cady Bush for everything, especially brightening up my days at the lab. I will miss your friendship and seeing your smiling face.

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I dedicate this dissertation to them.

Table of Contents

	Page
Abstract	iii
Acknowledgments	v
List of Figures	x
List of Tables	x
Chapter 1. Development of a domino Diels–Alder/Schmidt reaction en route to alkaloid-like skeleta.	1
Introduction	1
Efforts towards the development of a domino reaction	4
Preparation of diene and azido enone precursors	7
Diels–Alder/ Schmidt reaction controlled by segregation of the azide and ketone on separate molecules	10
Diels–Alder/Schmidt reaction controlled by deactivation	15
Summary	19
Chapter 2. Development of a novel domino Diels–Alder/acylation sequence for the synthesis of isoquinolinone scaffolds for library application	21
Introduction	21
Studies towards a new domino reaction	23
Synthesis of other dienes as domino reaction substrates	28

Mechanism and stereochemistry	34
Determination of dieneophile scope	38
Diversification of the isoquinolone scaffolds for compound library development	39
Summary	42
Chapter 3. Development of a first-generation catalytic Schmidt reaction	43
Introduction	43
The Schmidt reaction of ketones	43
Initial studies towards a catalytic Schmidt reaction	51
Synthesis of the necessary azidoketone Schmidt precursors	53
Development of conditions for a catalytic Schmidt reaction	60
Application of other azidoketones in this reaction sequence	64
The use of microwave irradiation in the Schmidt reaction	66
Summary	79
Chapter 4. Experimental Section	81
References	113

List of Figures

	Page
Figure 1. (a) Potential reactivity contained within maleic anhydride. (b) Isoquinolinone-type scaffold for diversity oriented synthesis applications.	22
Figure 2. X-ray crystal structure of (8 <i>R</i>)-2-(3,4-dichlorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid 47 .	33
Figure 3. The 2-(3'-azidopropyl)ketones prepared for study.	54
Figure 4. Other azidopropyl ketones prepared for methodology exploration.	56
Figure 5. Known dienes.	88
Figure 6. Known lactams, azidoketones and intermediates.	100

List of Tables

	Page
Table 1. Effect of Lewis acid on the reaction of 5 and cyclopent-2-enone.	12
Table 2. Diels–Alder reaction conditions in the microwave.	26
Table 3. Synthesis of amine-containing dienes.	31
Table 4. Isoquinolinone carboxylic acid scaffolds.	33
Table 5. Amines for preliminary library synthesis.	41
Table 6. Lactams synthesized using the intramolecular Schmidt reaction. ¹²	47
Table 7. Initial survey of conditions for a catalytic Schmidt reaction.	52

Table 8.	Lewis acid and solvent survey.	62
Table 9.	Lanthanide Lewis acid survey.	64
Table 10.	Lanthanide Lewis acid survey with phase transfer catalyst.	69
Table 11.	Results from catalytic Schmidt reaction.	72
Table 12.	Acyclic substrates from the standard Schmidt reaction.	78

Chapter 1

Development of a domino Diels–Alder/Schmidt reaction en route to alkaloid-like skeleta

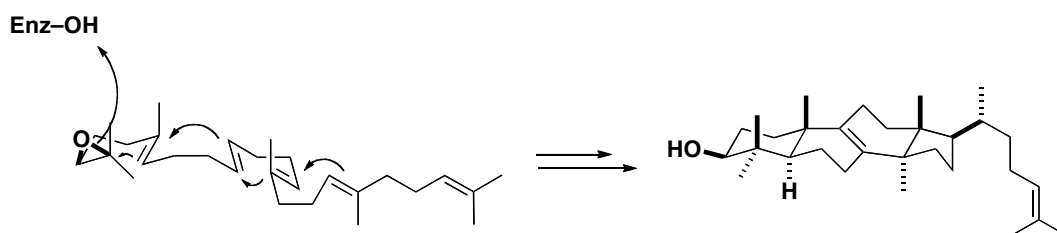
Introduction to domino reactions. Domino, tandem, or cascade reaction processes are important tools in the repertoire of a synthetic chemical researcher. Such reaction processes allow for multiple chemical transformations to occur within a single reaction vessel. Three hallmarks of a practical domino reaction are: high bond forming efficiency, increased structural complexity of products when compared to the starting materials, and finally suitability and practicality for general synthetic application.¹

Domino reaction sequences can be much more efficient than standard synthetic processes in which the formation of the product is accomplished through a stepwise formation of the individual bonds.² Nature utilizes domino reaction sequences quite frequently. However, these sequences differ significantly from those occurring within a flask at the bench. Nature has refined the individual enzymes necessary for each of its domino reactions through millennia of evolutionary pressure. These systems are highly ordered and significantly more complex than those contained within a flask at the bench. An impressive example of a domino reaction in nature is the biosynthesis of steroids from squalene epoxide (Scheme 1a). In this reaction, six stereogenic centers and four C–C bonds are formed leading to the

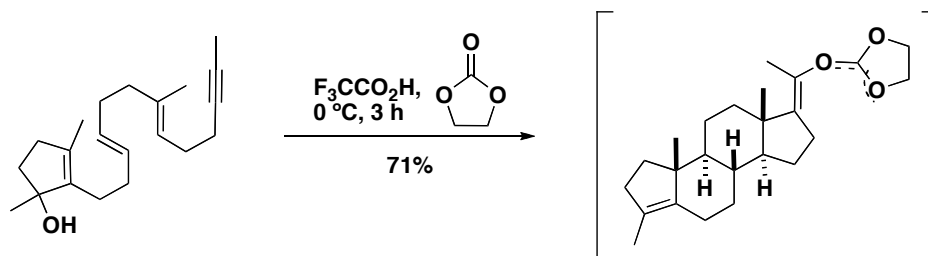
formation of lanosterol with high selectivity.³ Johnson later used this same concept in his biomimetic synthesis of progesterone. In this synthesis, he utilized an acid catalyzed domino reaction sequence to form the B, C, and D rings of progesterone in one pot (Scheme 1b).⁴

Scheme 1

(a)

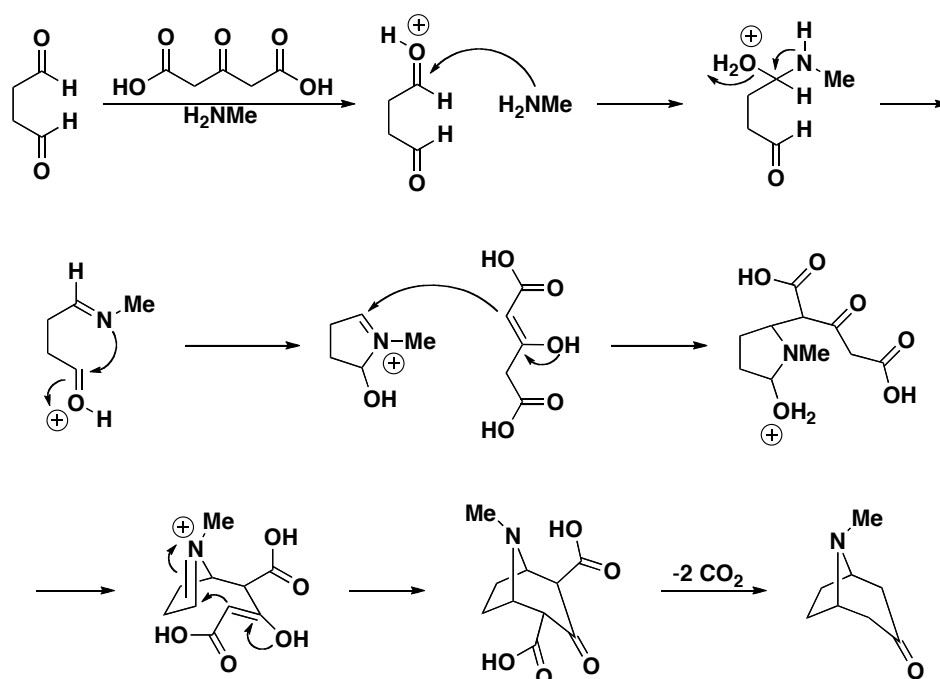


(b)



An early domino reaction used in the synthesis of a natural product was reported by both Robinson⁵ and Schöpf⁶ in 1917 and 1937, respectively. They combined succindialdehyde, methylamine, and acetonedicarboxylic acid to give a bicyclic tropinone (Scheme 2) via a double Mannich reaction.

Scheme 2

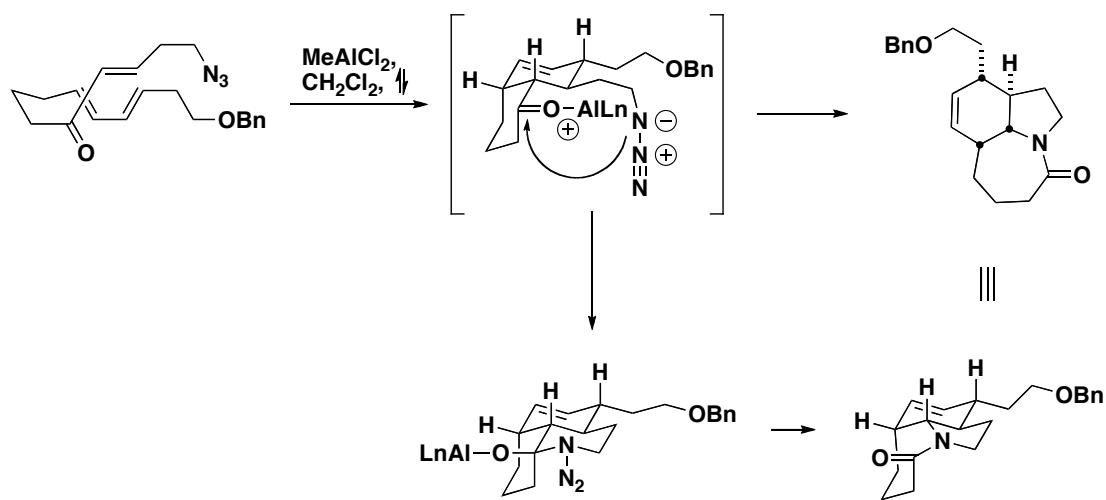


Some of the most powerful domino reactions use similar classical and robust carbon–carbon bond forming reactions, such as the Diels–Alder in combination with other carbon–carbon and carbon–heteroatom bond-forming reactions.⁷ Such processes are used to provide chemically complex and biologically interesting structures for further study.⁸ In particular, this laboratory has become interested in exploiting these types of reaction sequences to form interesting heterocycles as part of its ongoing efforts in broadening the scope of the Schmidt reaction.

The first such domino reaction was discovered in the course of carrying out the total synthesis of the alkaloid natural product stenine. In this work, Jennifer Golden prepared the triene shown and subjected it to methyl aluminum dichloride in

methylene chloride (Scheme 3). This led to a product resulting from a domino Diels–Alder/Schmidt reaction in good yield (79%).⁹ This product contained three of the four rings present in stenine; additionally, it established four of the necessary stereocenters in a single chemical step. This finding led to increased interest within the group to expand this chemistry into a viable methodology for future total synthesis and chemical library applications.

Scheme 3

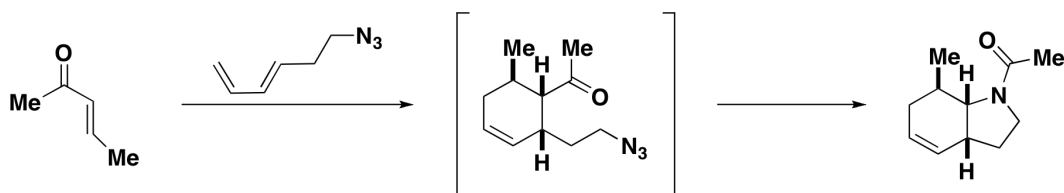


Efforts toward the development of a domino reaction. The development of a general Diels–Alder/Schmidt reaction sequence began with an analysis of other effective domino processes. We noted that the most successful of these methodologies utilize control over the various steps that comprise the complete transformation.¹⁰ Therefore, we determined that establishing control over the desired reactivity was necessary in order to devise an effective domino transformation.

The azido–Schmidt reaction is the protic or Lewis acid catalyzed transformation of an alkyl azide and a ketone to deliver a lactam product.^{11,12} Previous work showed the intermolecular Schmidt reaction of azides is less favored than the intramolecular version. Consequently, an intermolecular Schmidt reaction should not be able to compete with a facile Diels–Alder reaction.¹³ Thus, one strategy for controlling the order of events would be to segregate the ketone and azide on the dieneophile and diene, respectively (Scheme 4). This would utilize the Diels–Alder reaction to bring the two pieces together and only then would an intramolecular azido-Schmidt reaction take place.

Scheme 4

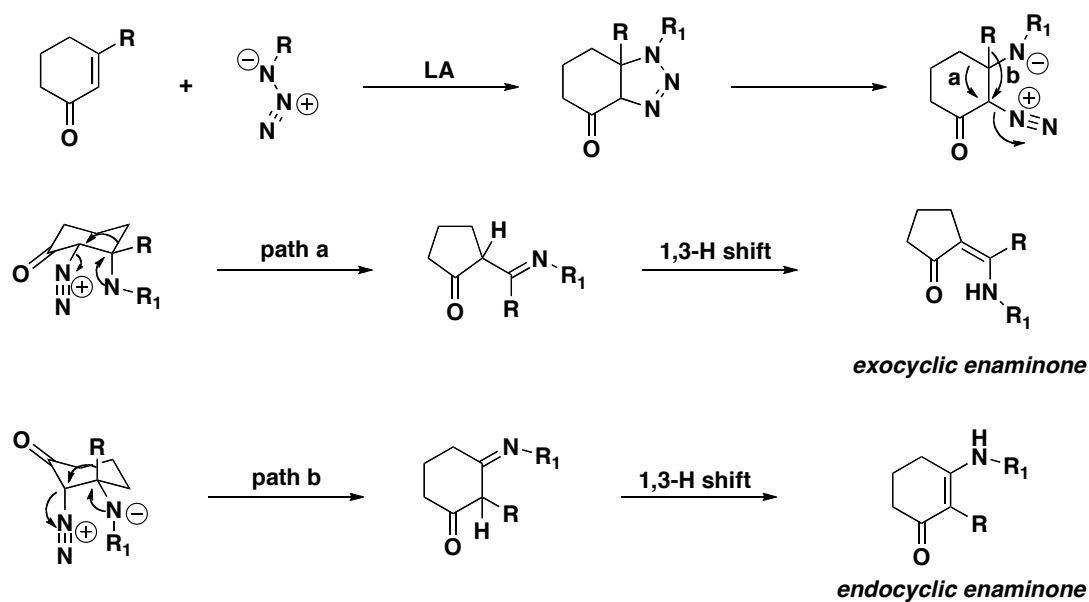
Intermolecular Diels–Alder + intramolecular Schmidt reaction



Another less obvious method works by “deactivating” the ketone functionality prior to the Diels–Alder cycloaddition. D. S. Reddy and Weston Judd have previously shown that enones rarely undergo even intramolecular azido-Schmidt reactions (Scheme 5).¹⁴ Under Lewis acid activation, such substrates often undergo regioselective 1,3-dipolar cycloaddition of the azide with the enone olefin to form a triazoline intermediate. This unstable species decomposes into one of two

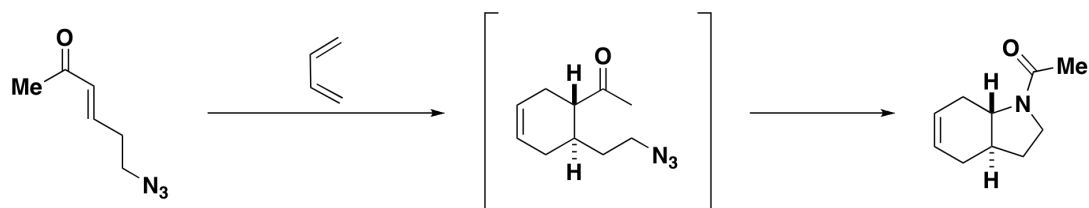
zwitterionic intermediates that lead to either a ring contracted exocyclic enaminone or an endocyclic enaminone. Moreover, an azide attached to an α,β -unsaturated ketone does not add to the enone and should not attack the carbonyl group until the conjugation has been eliminated through a Diels–Alder reaction (Scheme 6).

Scheme 5



Scheme 6

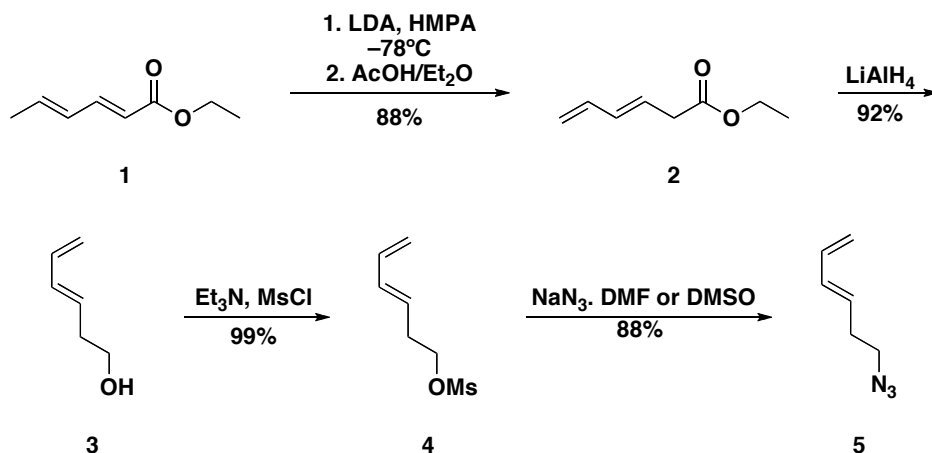
Enone deactivation method



In this thesis, I will describe how both approaches allow for the formation of a variety of complex heterocycles using efficient one-pot transformations. In order to begin these studies, it was first necessary to prepare the required reaction precursors.

Preparation of diene and azido enone precursors. The unactivated azido diene **5** could be obtained via literature precedent beginning with the known (*E*)-hexa-3,5-dienyl methanesulfonate **4** (Scheme 7).¹⁵ The methanesulfonate diene, obtained in 78% over three steps, was subjected to a simple S_N2 displacement reaction employing sodium azide in DMF or DMSO to give azide **5** in 88% yield.

Scheme 7

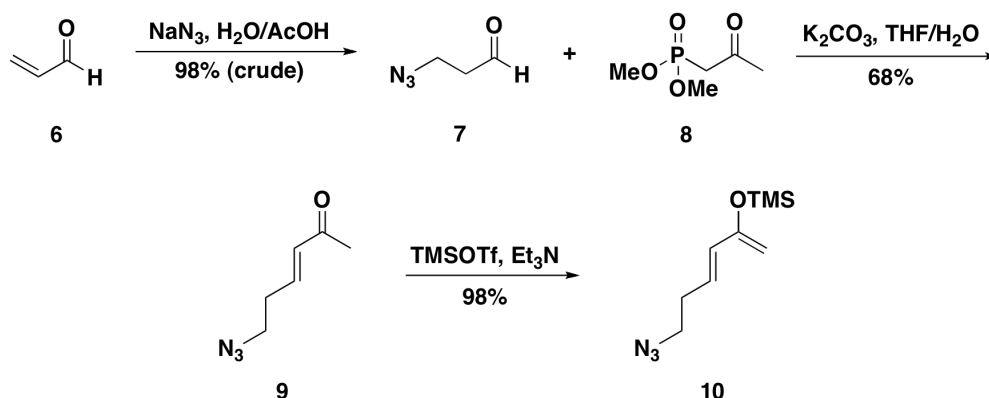


An activated azido diene, (*E*)-(6-azidohexa-1,3-dien-2-yloxy)trimethylsilane (**10**), was also prepared for investigation in this study (Scheme 8). The Michael addition of sodium azide to acrolein provided the azido aldehyde **7** in nearly

quantitative yield. The crude product was then used in the next step without further purification. It should be noted that this compound is a low molecular weight azide and is potentially explosive. Appropriate safety precautions were taken when isolating and handling this compound. These include avoiding heat when concentrating this compound under vacuum, using safety shields and the appropriate eye and hand protection, as well as avoiding the isolation of large quantities of pure material.

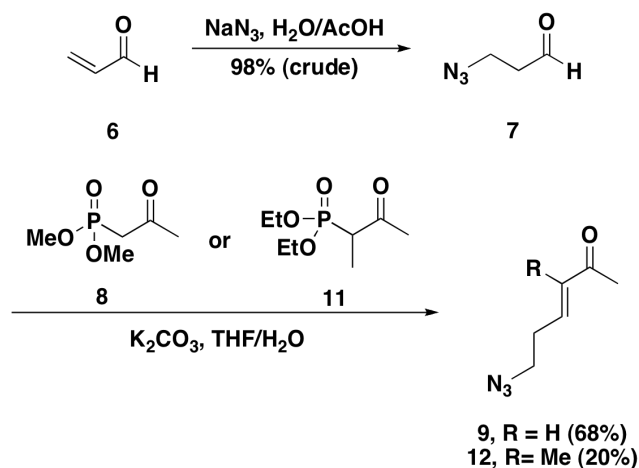
The second step in this scheme was the formation of the necessary (*E*)-6-azidohex-3-en-2-one (**9**). This was accomplished via a Horner–Wadsworth–Emmons condensation of the azido aldehyde **7** with commercially available dimethyl-2-oxopropylphosphonate (**8**) to form the (*E*)-azido enone **9**, which was obtained in a moderate 68% yield. The residual mass balance of the reaction consisted of azide elimination product. The azido enone product isolated from this reaction is also volatile and product loss was observed during concentration. Purification using column chromatography gave the pure (*E*)-azido enone **9**, which was subsequently reacted with TMSOTf in the presence of NEt₃. The (*E*)-(6-azidohexa-1,3-dien-2-yloxy)trimethylsilane (**10**) was formed in near quantitative yields (98%) and was used without further purification as a reactant for the domino reaction.

Scheme 8



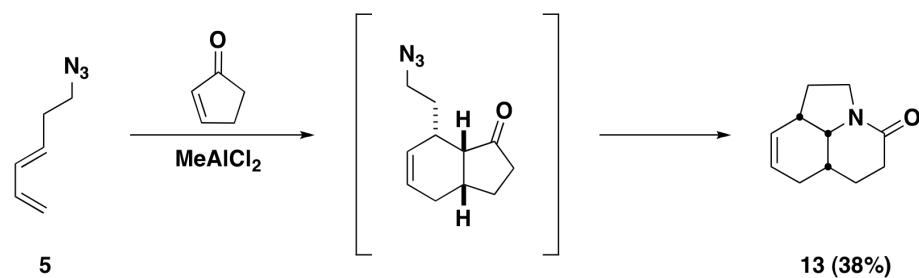
For the second approach to the domino Diels–Alder/Schmidt reaction utilizing an enone deactivation method, we synthesized two acyclic azido enones as starting materials (Scheme 9). Thus, **9** and **12** were synthesized in two steps from acrolein in a similar manner to silyloxydiene **10**. This synthesis began with a Michael addition into acrolein and was followed by a Horner–Wadsworth–Emmons reaction with either dimethyl 2-oxopropylphosphonate (**8**) or diethyl 3-oxobutan-2-ylphosphonate (**11**) to afford **9** and **12**. (*E*)-6-azido-3-methylhex-3-en-2-one (**12**) was prepared by Reddy and Zeng and isolated in 20% yield.

Scheme 9



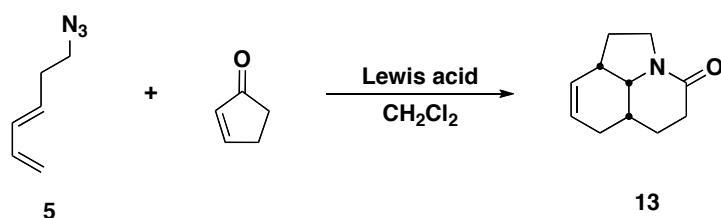
Diels–Alder/Schmidt reaction controlled by segregation of the azide and ketone on separate molecules. A typical early experiment, as reported¹³ by D. Srinivas Reddy and Yibin Zeng, utilized (*E*)-6-azido-1,3-hexadiene (**5**) and cyclopentenone, and proceeded as follows. The enone was added to a solution of diene in methylene chloride and the reaction mixture was cooled to $-78\text{ }^\circ\text{C}$. Then 2.0 equiv of MeAlCl_2 were added to the cooled reaction mixture, which was stirred for two hours at this temperature. After being allowed to warm to room temperature the reaction was allowed to stir for an additional 12 hours. Upon workup, this provided the tricyclic lactam product **13** in a modest yield of 38% (Scheme 10).

Scheme 10



A limited set of Lewis acids for promoting the domino reaction with (*E*)-6-azido-1,3-hexadiene (**5**) was examined which included aluminum-, boron-, titanium-, and zinc-based reagents (Table 1). As the table shows, the best results were obtained with aluminum-based reagents in dichloromethane.

Table 1. Effect of Lewis acid on the reaction of **5** and cyclopent-2-enone.

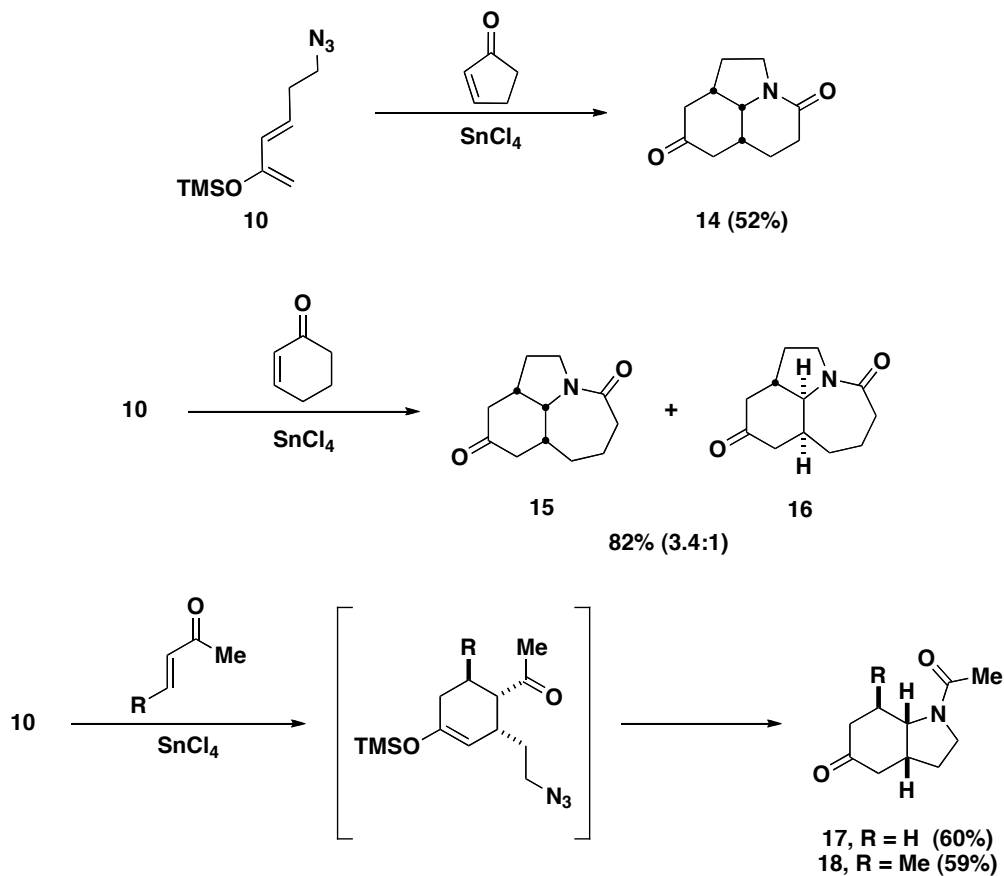


entry	Lewis acid	yield
1	2 equiv MeAlCl_2	38%
2	1 equiv $\text{BF}\cdot\text{Et}_2\text{O}$	No reaction
3	1 equiv $\text{TiCl}(\text{O}-i\text{Pr})_3$	No reaction
4	1.4 equiv TiCl_4	23%
5	1 equiv TMSOTf	15% triazole
6	0.65 equiv ZnCl_2	SM

The modest success afforded by the methyl aluminum dichloride promoted reaction of the unactivated azido diene **5**, led us to examine the reaction sequence using the more electron-rich azido diene **10**. We hypothesized that the increased electron donating capacity of the added silyloxy group would allow for greater reactivity between the diene and dieneophile reaction components. (*E*)-(6-Azidohexa-1,3-dien-2-yloxy)trimethylsilane (**10**) was employed in reactions with several cyclic and acyclic enones (Scheme 11). Furthermore, in experiments with this diene, 2.5 equivalents of tin tetrachloride (SnCl_4) was determined to be superior to methyl aluminum dichloride (MeAlCl_2) in promoting the domino reaction. As expected,

reactions that utilized the more electron-rich diene afforded higher yields of the desired bi- and tricyclic lactams.

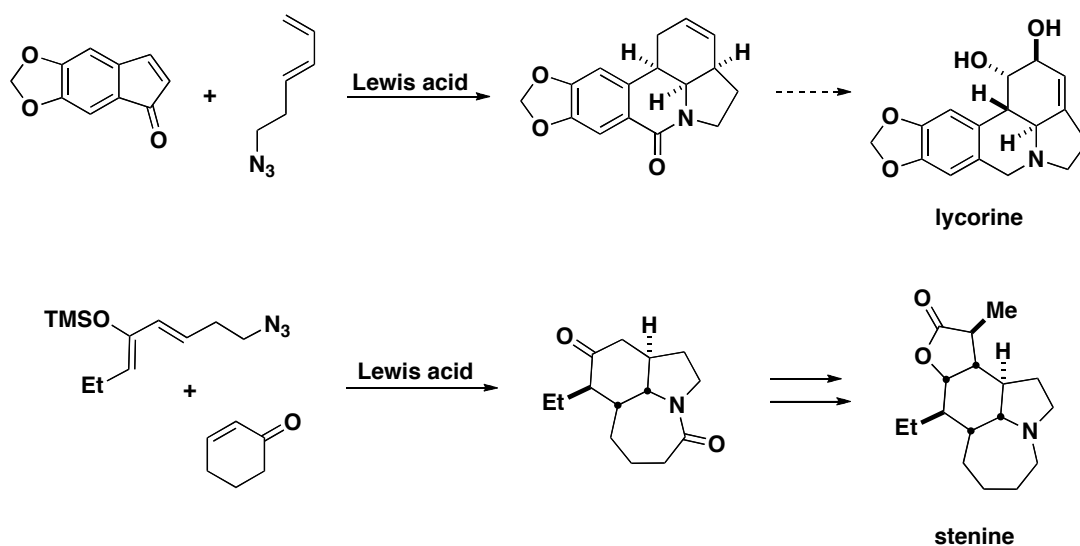
Scheme 11



This domino reaction sequence provides an expedient and effective synthetic route to skeleta which resemble many nitrogen-containing natural products, such as the stemona (e.g. stenine and neotuberostemonine) and the lycorine alkaloids (e.g. lycorine and lycorane) (Scheme 12).^{17,18} We were also able to obtain pyrroloisoquinolones, perhydroindoles, and azipinoindolones in good yields and high

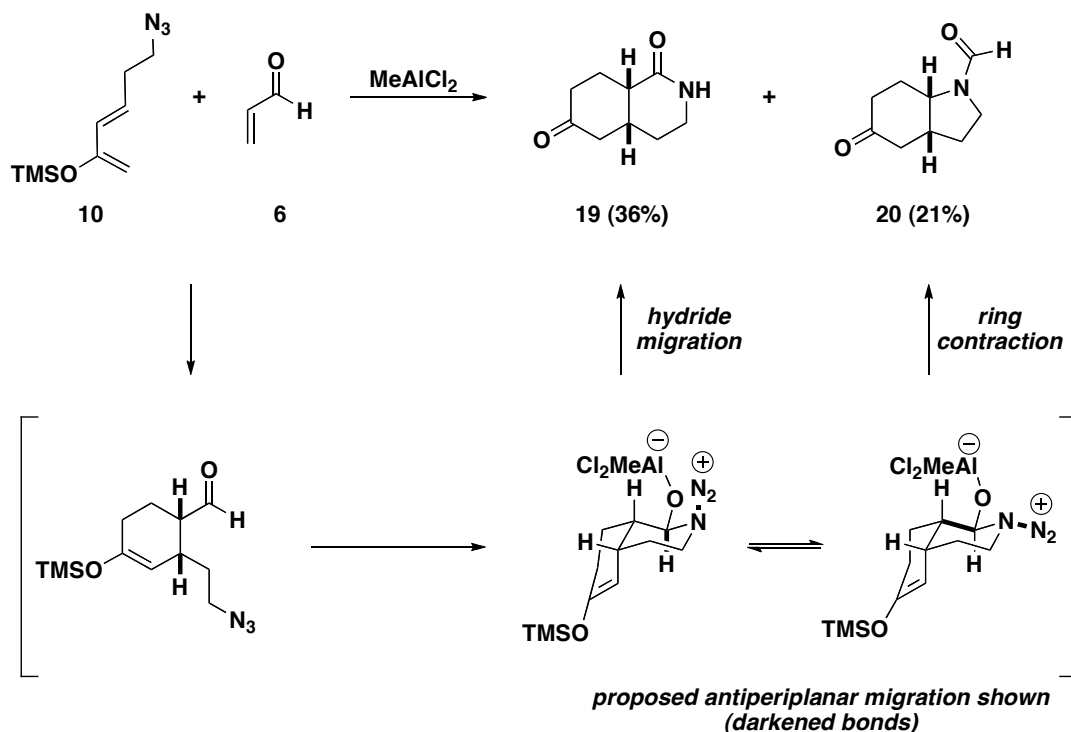
diastereoselectivity. Furthermore, the relative stereochemistry of each isolated heterocycle was determined using NOESY studies. These experiments demonstrated that the domino reaction proceeds through an *endo*-selective Diels–Alder reaction, which is then followed by a stereoselective Schmidt ring expansion reaction.

Scheme 12



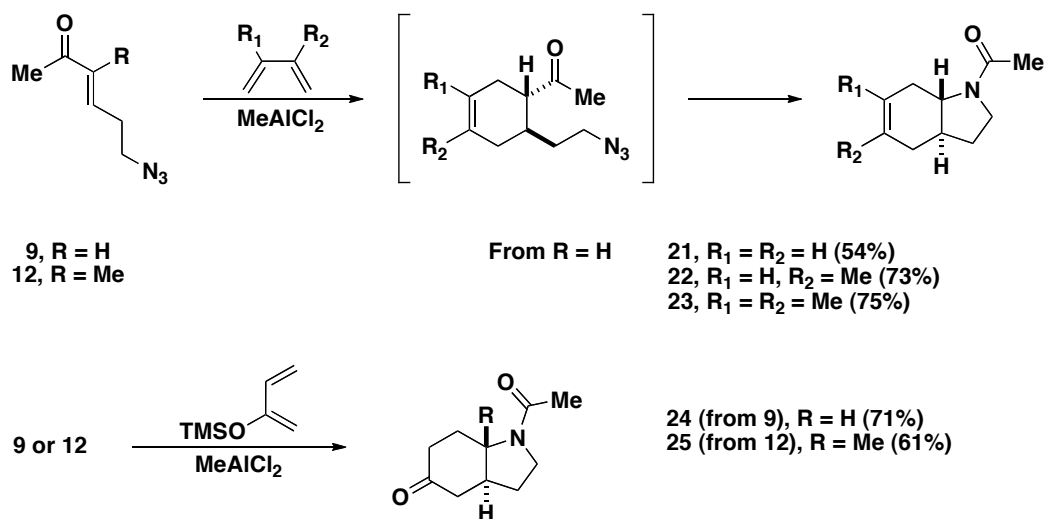
Yibin Zeng utilized the silyloxydiene **10** in a further reaction that provided an interesting result. It was determined that the reaction of this diene with acrolein yielded two isomeric products, the decahydroisoquinoline **19** and the perhydroindole **20** (Scheme 13). These presumably arise from a hydride migration and a ring contraction, respectively.

Scheme 13



Diels–Alder/Schmidt reaction controlled by deactivation. To test our hypothesis regarding deactivation of the ketone to facilitate the domino reaction, the prepared azido enone **9** in methylene chloride was treated with 1,3-butadiene and cooled to 0 °C. Then 2.5 equivalents of MeAlCl_2 were added to the flask. The mixture was stirred at this temperature and then allowed to warm to room temperature over several hours to give the desired Diels–Alder/Schmidt adducts (Scheme 14). Various substituted dienes were examined in this reaction sequence, including mono- and disubstituted butadienes and other more electron-rich dienes such as 2-(trimethylsilyloxy)-1,3-butadiene.

Scheme 14

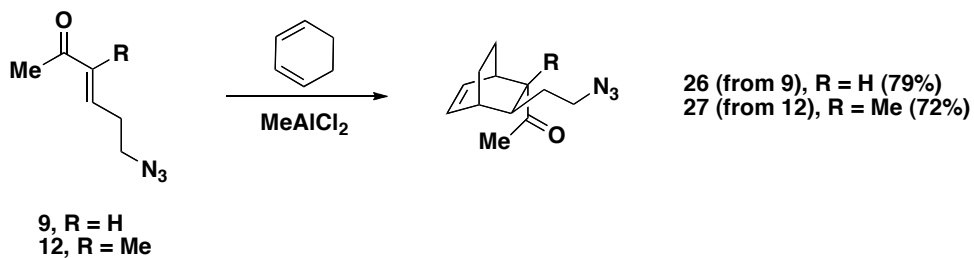


The product *trans*-hexahydroindoles (**21–25**) were obtained in good yields (54–75%) following chromatography. Other acyclic enones were also investigated to study substitution patterns tolerated by the reaction. The first of these used a simple methyl substitution on the previously described enone. Reddy and Zeng then treated enone **12** with 2-(trimethylsiloxy)-1,3-butadiene as shown in Scheme 14. Azido enone **12** participates in the reaction to provide **25** in slightly diminished yields, 61% versus 71% in the unsubstituted version.

A limitation of the methodology was found when Yibin Zeng and D. S. Reddy reacted acyclic azidoenones **9** and **12** with a cyclic diene, specifically 1,3-cyclohexadiene. While the diene reacted with both azido enones **9** and **12** in a Diels–Alder reaction to give the bridged bicyclic Schmidt precursors **26** and **27** in yields of 79% and 72%, respectively, the subsequent Schmidt reaction did not occur. We postulate that this is due to the rigid *trans* orientation of the resulting ketone and azide

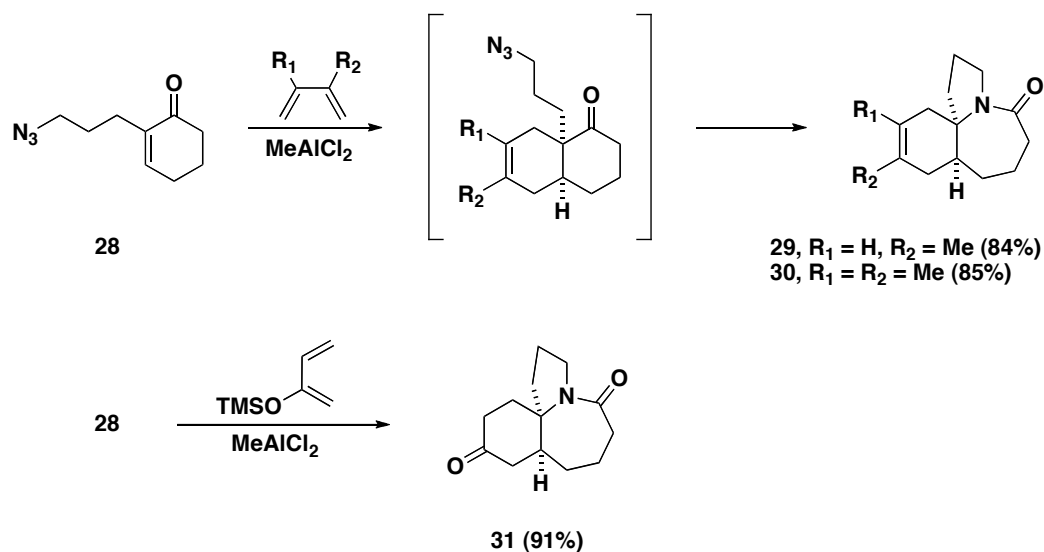
moieties on the Diels–Alder adducts (Scheme 15), which would prevent the side chains from achieving the necessary alignment for the Schmidt reaction to occur.

Scheme 15



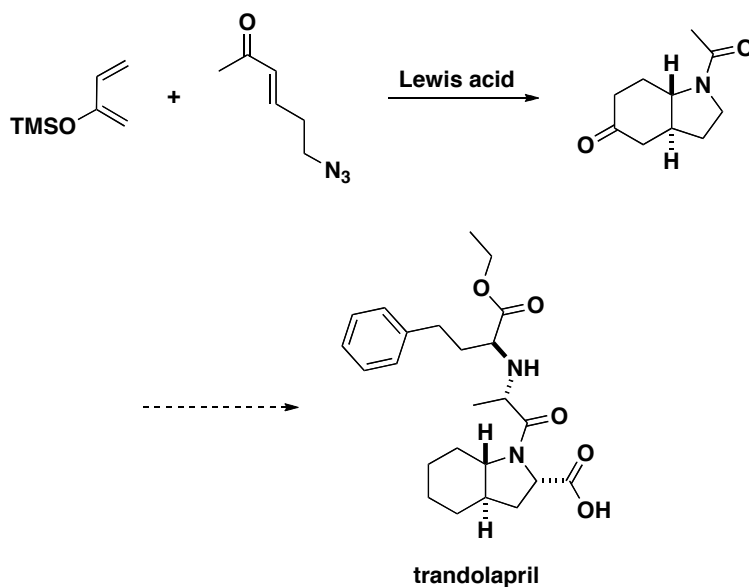
As a further exploration of the limits of this transformation Reddy and Zeng examined a cyclic azido enone. This cyclohexyl azido enone **28**, previously prepared by Milligan and Mossman,¹² was submitted to the standard reaction conditions using MeAlCl_2 and the acyclic dienes used previously (Scheme 16). The reactions afforded the tricyclic lactams, homopyrrolo[2,1-*j*]quinolin-5-ones **29–31** in excellent yields (84-91%). The structure of **31** was confirmed by X-ray crystallographic analysis.

Scheme 16



The development of this second type of domino Diels–Alder/Schmidt reaction by masking the azido-ketone via deactivation has allowed for the formation of additional biologically interesting heterocycles such as the *trans*-hexahydroindoles and homopyrrolo[2,1-*j*]quinolin-5-ones (Scheme 17). These ring systems appear in some natural products and medicinally useful compounds, for example the known angiotensin-converting enzyme (ACE) inhibitor trandolapril.¹⁸

Scheme 17



Summary. Since completing this study, the Diels–Alder/Schmidt reaction has been further applied to natural product synthesis, specifically towards the stenine family of alkaloids, and structurally related libraries.^{19,20}

This project allowed us to examine the feasibility of pairing the azido-Schmidt reaction in tandem with the Diels–Alder reaction via two different conceptual methods. The first of these relied upon using the azide and ketone moieties on two different substrates, thereby ensuring that the Diels–Alder reaction occurred first. The second method exploited previous results from our group, in which it was determined that α,β -unsaturated ketones do not readily participate in the azido-Schmidt reaction. This allowed for another means to control the order of reaction steps. In this way, it was possible to demonstrate the promise of the azido-Schmidt reaction in preparing biologically interesting heterocycles in combination with other Lewis acid-mediated

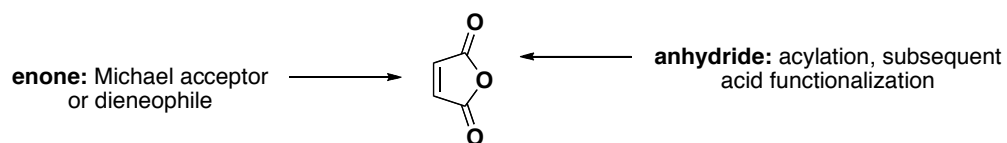
processes. The successful development of this methodology spurred our interest in discovering other novel domino reactions for the formation of nitrogen containing heterocycles.

Chapter 2

Development of a novel domino Diels–Alder/acylation sequence for the synthesis of isoquinolinone scaffolds for library application.

Introduction. As part of our continued research efforts into the development of novel domino reaction sequences, we have begun to focus some of our efforts towards reactions that utilize compact, reactivity-packed molecules such as maleic anhydride (Figure 1a).^{13,20,21} We note that within the maleic anhydride structure there are several important functional groups, which could be used as chemical “handles” or diversification sites to react with other functionalities. The ability to manipulate this reactivity with some control permits interesting chemical transformations to occur. Our interest in this molecule stems from our desire to form novel and interesting heterocyclic scaffolds for methodology development and biological screening.

a)



b)

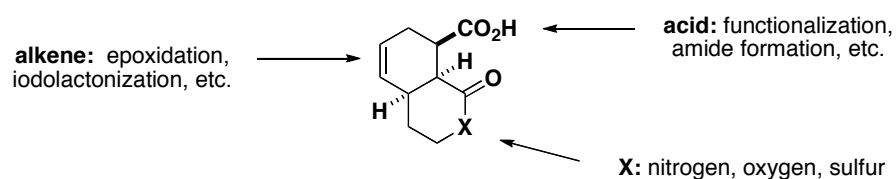
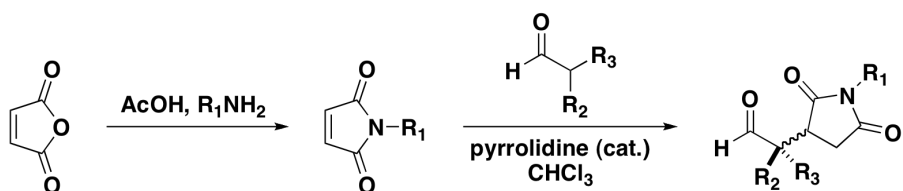


Figure 1. (a) Potential reactivity contained within maleic anhydride.

(b) Isoquinolinone-type scaffold for diversity oriented synthesis applications.

Maleic anhydride contains a conjugated double bond that could react with nucleophiles as a Michael acceptor. A related example was reported by Nöth and Reiser,²¹ in which maleimides were substrates for a Michael addition of an enamine nucleophile formed in situ from an α, α -disubstituted aldehyde (Scheme 18).

Scheme 18



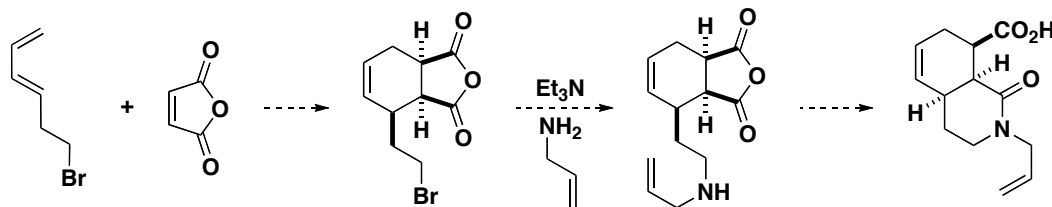
This same double bond could also participate as a dieneophile in a Diels–Alder reaction sequence. This reactivity is known and is widely reported in the chemical literature.²² Furthermore, the anhydride portion of the molecule is yet another possible reactive site. The carbonyl functionality is activated for acylation and subsequent acid functionalization. The initial goal of this project was to develop a synthetic route that would provide convenient access into an interesting family of heterocyclic compounds (Figure 1b). These heterocycles would also contain available diversification sites on the molecule for further functionalization as part of our continued interest in library construction.^{8,20} While molecules of this type containing oxygen and nitrogen atoms are known, we also had interest in a variety of ring sizes for the lower heterocyclic ring such as 5, 6, and 7 membered rings as part of our studies into molecules of this type.²⁴

Studies towards a new domino reaction. To begin our investigations into these types of structures we decided to first examine systems containing nitrogen atoms. Nitrogen-containing heterocycles are of great interest to this group from our previous work in the development and study of the Schmidt reaction.^{9,11-13,20,21} We envisioned that a Diels–Alder reaction combined with a transacylation reaction of the resulting imide group would allow expeditious entry into some of the desired scaffolds noted above (Figure 1) using known starting materials. A literature search showed that while the general isoquinolinone scaffold was known²³ and that there were a few examples of isoquinol-5-ones formed through Diels–Alder reactions,²⁴

there were no known examples of domino strategies to form the N-alkyl-octahydroisoquinolin-1-one-8-carboxylic acid scaffolds.²⁵

First, the reaction between maleic anhydride and a halogenated diene was investigated (Scheme 19). Thus, we expected the Alder endo rule to prevail, resulting in the halogenated side chain being positioned *cis* to a reactive carbonyl group. We then hoped that further reaction with a primary amine would afford displacement of the halogen and subsequent transacylation of the amine into the reactive carbonyl moiety.

Scheme 19

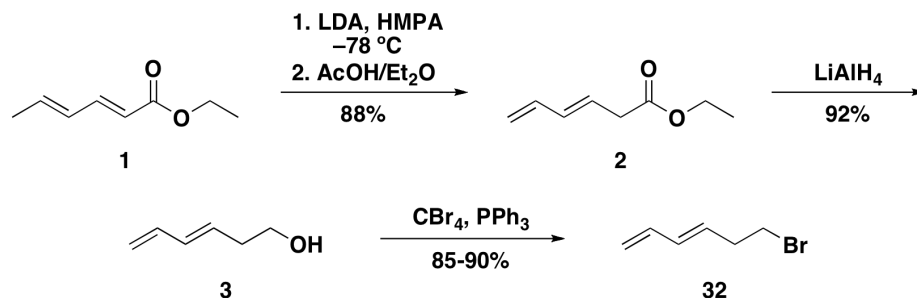


The known bromodiene **32** was first prepared from commercially available ethyl sorbate (Scheme 20).^{15,26,27} Using the general procedure of Batey and coworkers²⁶ deconjugation was accomplished by treatment of ethyl sorbate with lithium diisopropyl amide, formed in situ, at $-78\text{ }^{\circ}\text{C}$, in the presence of excess HMPA. The reaction was then quenched at $-78\text{ }^{\circ}\text{C}$ to provide the deconjugated diene **2** in good yield (88%). If the reaction was allowed to warm up before it was quenched, equilibration of the dienes occurred giving a mixture of products. The

crude deconjugated ester was then taken on to the next reaction without further purification.

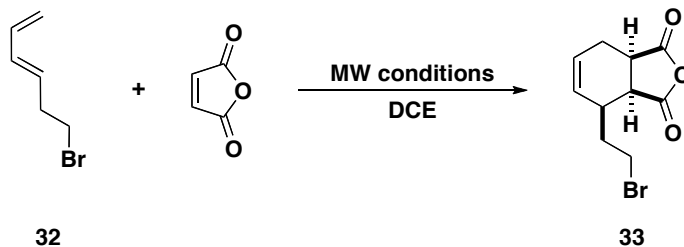
Reduction of the deconjugated ester **2** with lithium aluminum hydride in diethyl ether furnished the alcohol **3** in good yield using a water, 10% sodium hydroxide solution, and water workup.²⁸ Subsequent reaction of the alcohol with carbon tetrabromide and triphenylphosphine gave the desired alkenyl bromide **32** in good yields (85-90%).²⁹

Scheme 20



Having in hand a scalable synthesis of the alkenyl bromide **32**, we began to investigate conditions for Diels–Alder reactions using microwave irradiation. After a brief study of the reaction by Yibin Zeng and Robyn Allyn, it was determined that a 2.5:1 ratio of bromide to anhydride in DCE reacted at 165°C for 60 minutes allowed for complete conversion of the starting material into the desired Diels–Alder adduct **33**, as determined by NMR (Table 2).

Table 2. Diels–Alder reaction conditions in the microwave.



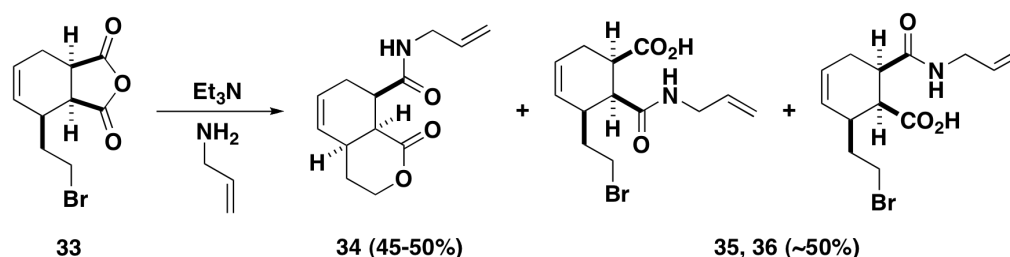
entry	bromide:anhydride	bromide [M]	Time (min)	Temp (°C)	Conv. (%) ^a
1	1:1	neat	10	190	<5
2	1:1	0.62	10	180	19
3	1.5:1	1.24	60	165	50
4	2:1	0.62	30	180	20
5	2.5:1	0.62	60	165	>95

^aNMR calculation

Once we had determined appropriate conditions for running the Diels–Alder reaction using microwave irradiation, we began exploring the formation of the desired isoquinolinone scaffolds envisioned in Figure 1. These experiments, performed by Robyn Allyn and Yibin Zeng, provided the endo Diels–Alder adduct as a single isomer, in good yield. The stereochemistry of the product was not determined, but was assumed to be *cis-syn cis*. Accordingly, we reacted Diels–Alder adduct **33** with allyl amine in an attempt to displace the bromide. We hoped that upon displacement

the amine would subsequently participate in an acylation reaction with the carbonyl group nearest to it affording the desired isoquinolinone product. Instead, we observed that the allyl amine added preferentially into both carbonyl groups on the anhydride. This reaction did not provide us with the scaffold that we desired. Moreover, it proved non-selective. The products from this reaction included opening of the anhydride by the primary amine at both carbonyls **35** and **36** (ca. 50%), and subsequent closure of the opened anhydride to form a lactone **34** (ca. 45-50%) as shown in Scheme 21.

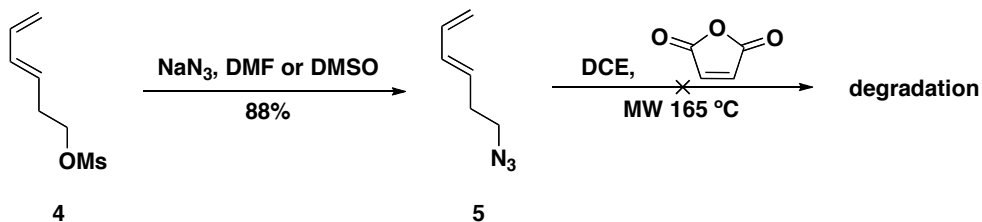
Scheme 21



Since we were unable to gain entry into the isoquinolinone scaffolds using this method, we wanted to investigate their formation through the use of other nucleophiles on the diene. Robyn Allyn then made the known azido diene **5**, using the mesylated alcohol **4** as described in chapter 1 (Scheme 7).¹⁵ We proceeded to examine azido diene **5** in the Diels–Alder reaction. The reaction was done as described above for the synthesis of the Diels–Alder adduct **33**. Again, none of the

desired isoquinolinone product from this reaction was observed. Instead, degradation of azido diene **5** occurred (Scheme 22).

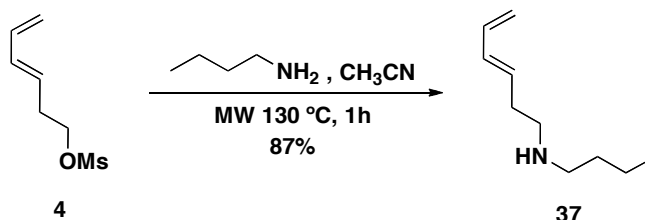
Scheme 22



Synthesis of other dienes as domino reaction substrates. Next we decided to examine an amine-containing diene as a potential reactant for the synthesis of the isoquinolinone scaffold. Yet again we utilized mesylate **4** to synthesize the desired amino dienes via a displacement strategy published by Metz and coworkers.¹⁵ We investigated multiple conditions for making the amino dienes, and found several which worked quite reliably and provided the desired amines in good yields (78–97%). These approaches utilized microwave irradiation to facilitate the reaction at 130 °C for 1 hour; later it was determined that placing the reagents into a sealed tube at 65 °C for 19 hours would also effect this transformation. The virtue of the microwave irradiation method was the shorter reaction times and overall convenience. For later studies and library development we moved to the sealed tube method as it was determined to be more easily scalable for the larger quantities necessary for scaffold production.

A typical reaction for the amine formation was set up as described for our initial test substrate, (*E*)-*N*-butylhexa-3,5-dien-1-amine (**37**) (Scheme 23). To a clean microwave vial equipped for stirring was added the mesylate **4** followed by butylamine and acetonitrile. The vial was subsequently capped and irradiated in the microwave for 1 hour at 130 °C. Then the reaction was partitioned between aqueous NaOH and ether. The organics were dried (Na₂SO₄), the solvent removed in vacuo, and the residue purified by silica chromatography to give the (*E*)-*N*-butylhexa-3,5-dien-1-amine (**37**) in 87% yield.

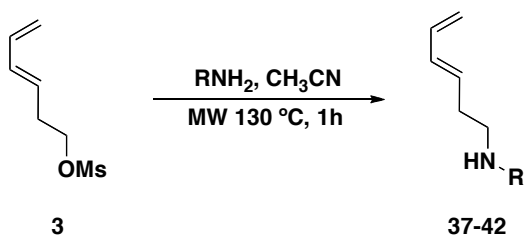
Scheme 23

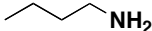
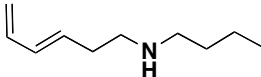
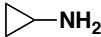
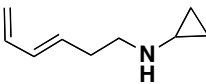
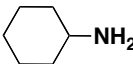
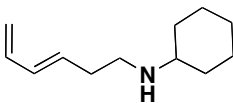
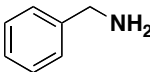
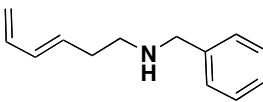
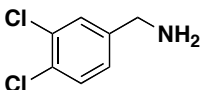
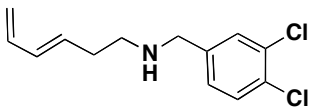
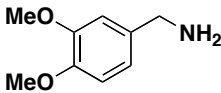
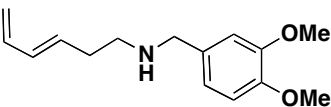


It was determined that even a small amount of the primary amine retained from the amine displacement reaction would inhibit the subsequent Diels–Alder/acylation reaction sequence. Therefore, it was necessary that the amino diene components be pure before submitting them to the domino reaction sequence. We ultimately determined that carrying out column chromatography using a slow gradient column of hexanes and increasing amounts of ethyl acetate (10–50%) sufficiently purified the amino dienes for use in the domino reaction sequence. This method was used to prepare five other amino dienes (**38–42**) from variously substituted primary

amines. We selected these amines to encompass a range of structural and stereoelectronic diversity including straight chain, branched, and cyclic alkyl groups as well as neutral, electron withdrawing, and electron donating aryl groups for this methodology study (Table 3). All of the amino dienes were synthesized in moderate to good yields using the same method described for (*E*)-*N*-butylhexa-3,5-dien-1-amine (**37**).

Table 3. Synthesis of amine-containing dienes.

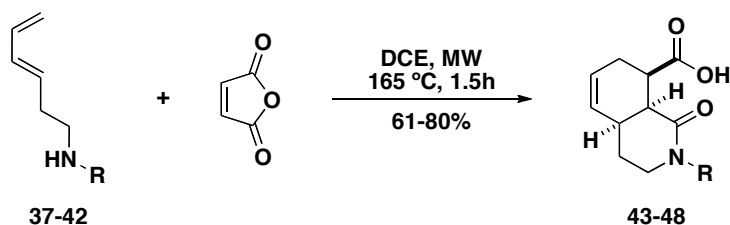


entry	amine	product	cmpd	yield (%)
1			37	87
2			38	40
3			39	78
4			40	92
5			41	97
6			42	80

Upon isolating pure (*E*)-*N*-butylhexa-3,5-dien-1-amine (**37**) we attempted to perform a domino Diels–Alder/acylation reaction by reacting this substrate with maleic anhydride in dichloroethane (DCE) (Scheme 24). The reaction was performed in a clean, oven-dried 2-5 mL microwave vial to which was added the amino diene **37**, followed by dichloroethane and maleic anhydride. This mixture was capped and

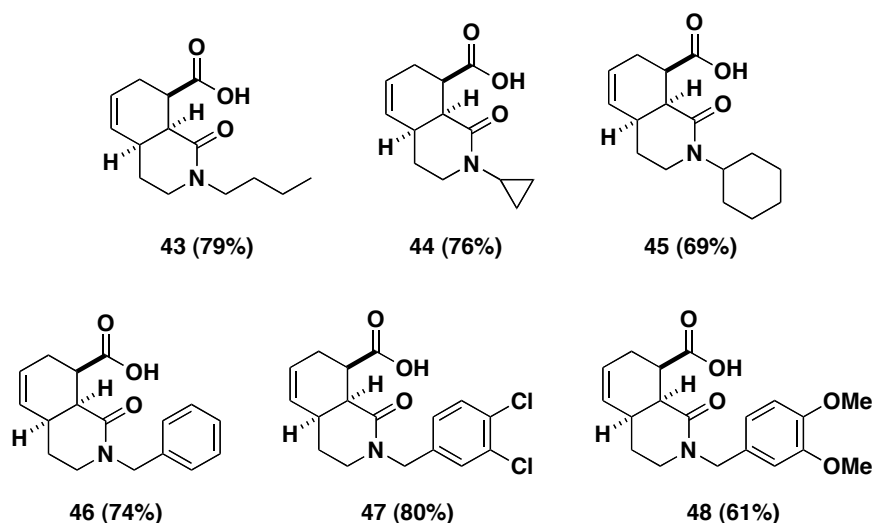
heated to 165 °C for 1.5 hours. Following flash chromatography, the desired isoquinolinone **43** was obtained as the sole product in 74% yield. This positive result was encouraging and led us to further investigate these findings.

Scheme 24



Having determined that the domino Diels–Alder/acylation sequence was a viable reaction path for forming the desired isoquinolinones, we examined the other amino dienes synthesized in this reaction sequence (Table 4) to better understand the limitations and breadth of this new chemical methodology. The amino dienes (**38–42**) participated in the reaction under these general conditions to provide five additional isoquinolinones (**44–48**) that could be further diversified for making our initial compound libraries.

Table 4. Isoquinolinone carboxylic acid scaffolds.



The isoquinolinone carboxylic acids were isolated after reaction of the amino diene with maleic anhydride, and were, with one exception, purified by column chromatography.

(8*R*)-2-(3,4-Dichlorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (**47**) was the exception, as this compound crystallized directly from the reaction mixture in good yield and excellent purity. Compound **47** was recrystallized from hexanes:ethyl acetate and afforded X-ray quality crystals from which we unambiguously assigned the relative stereochemistry of the isoquinolinone carboxylic acids (Figure 2). Determining suitable conditions for isolation of the other five compounds required some optimization. Ultimately, the method determined to work most efficiently for this purpose was the moist ether chromatography system developed by Taber and coworkers.³⁰ This chromatography eluent system for acids is prepared by adding 90 mL of ether to 10 mL of 0.5M monobasic (pH = 4.0) phosphate buffer, and 1 mL of glacial acetic acid in a

separatory funnel. The solvents are shaken and the layers separated. The ether layer that you separate from this extraction is then ready for chromatography. Use of this method in the present instance provided the desired compounds in good yields and high purities.

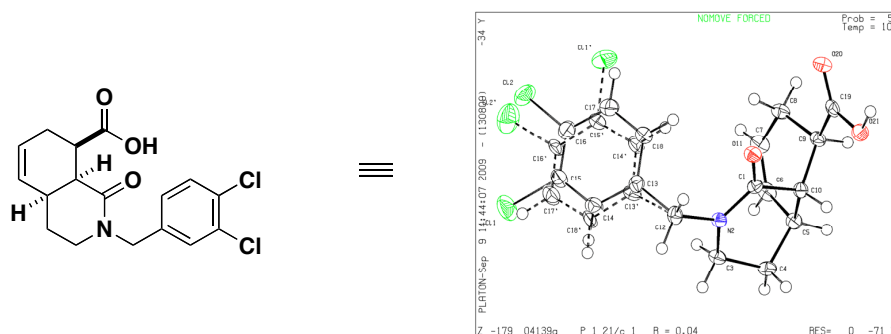
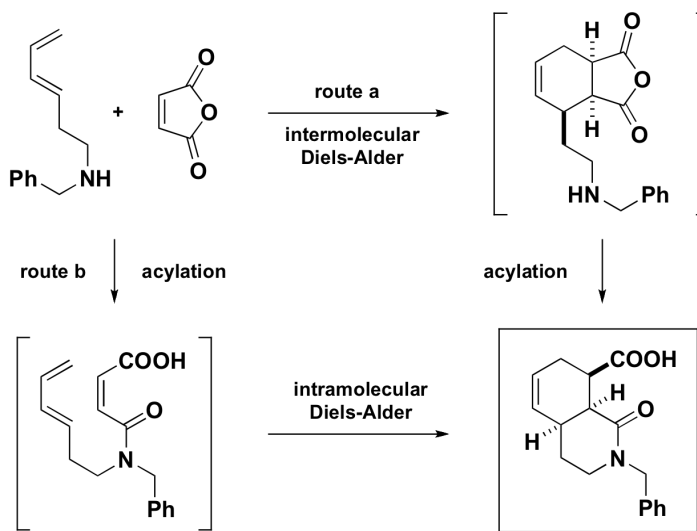


Figure 2. X-ray crystal structure of (8*R*)-2-(3,4-dichlorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (**47**).

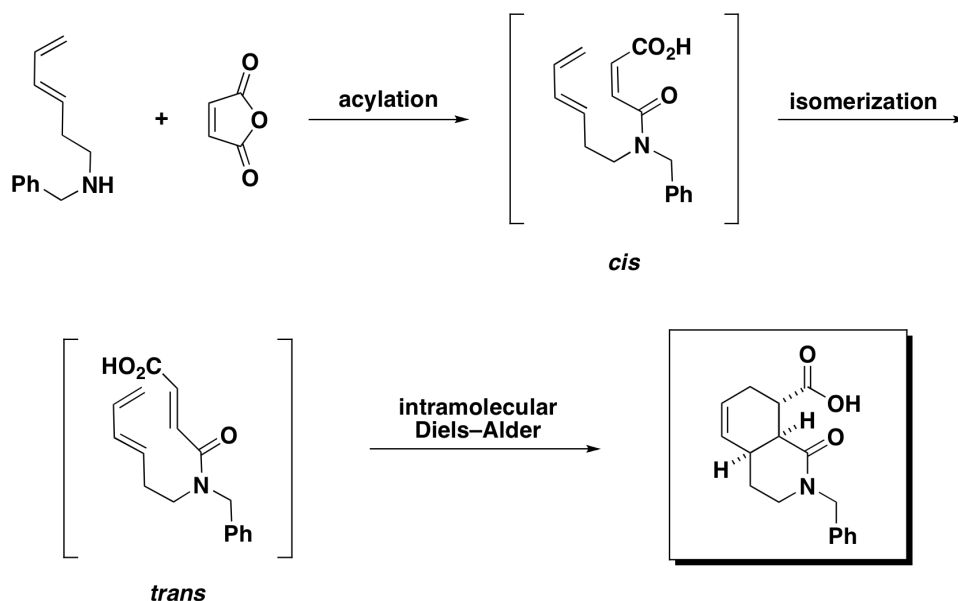
Mechanism and stereochemistry. The Diels–Alder/acylation sequence could occur through two different reaction pathways. Thus, one could envision the process first proceeding through a Diels–Alder reaction and subsequently an acylation reaction. However, one could also envision the reaction sequence occurring first via an acylation to open the maleic anhydride ring system bringing the two components of the reaction into a favorable position for the ensuing intramolecular Diels–Alder reaction (Scheme 25).

Scheme 25

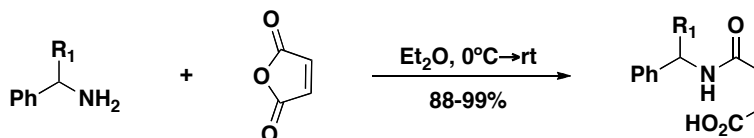


If the acylation reaction were to occur first, stereochemical scrambling could occur before the cycloaddition step (Scheme 26). Thus, the olefin in maleic anhydride is locked into the *Z*-form. Upon acylation, the ring opens and reveals an α,β -unsaturated carboxylic acid, which could in principle undergo isomerization to give the more thermodynamically favored *E*-substituted olefin. If the subsequent Diels–Alder reaction does not occur faster than the possible isomerization, then the isomer shown in Scheme 26 could be formed. However, the kinetics of such an isomerization process are known, and the reaction is unfavorable under our conditions.³¹ In addition, Garner and coworkers have demonstrated that maleic anhydride undergoes acylation with retention of the *cis* stereochemistry (Scheme 27).³² Under our conditions we exclusively see the product resulting from reaction of the *Z*-olefin, which is consistent with either order of reaction.

Scheme 26



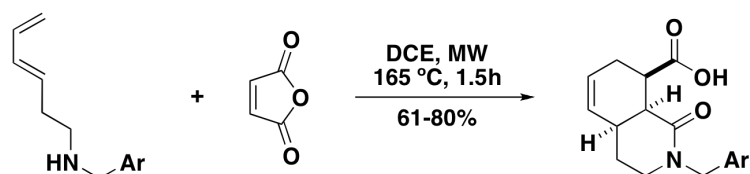
Scheme 27



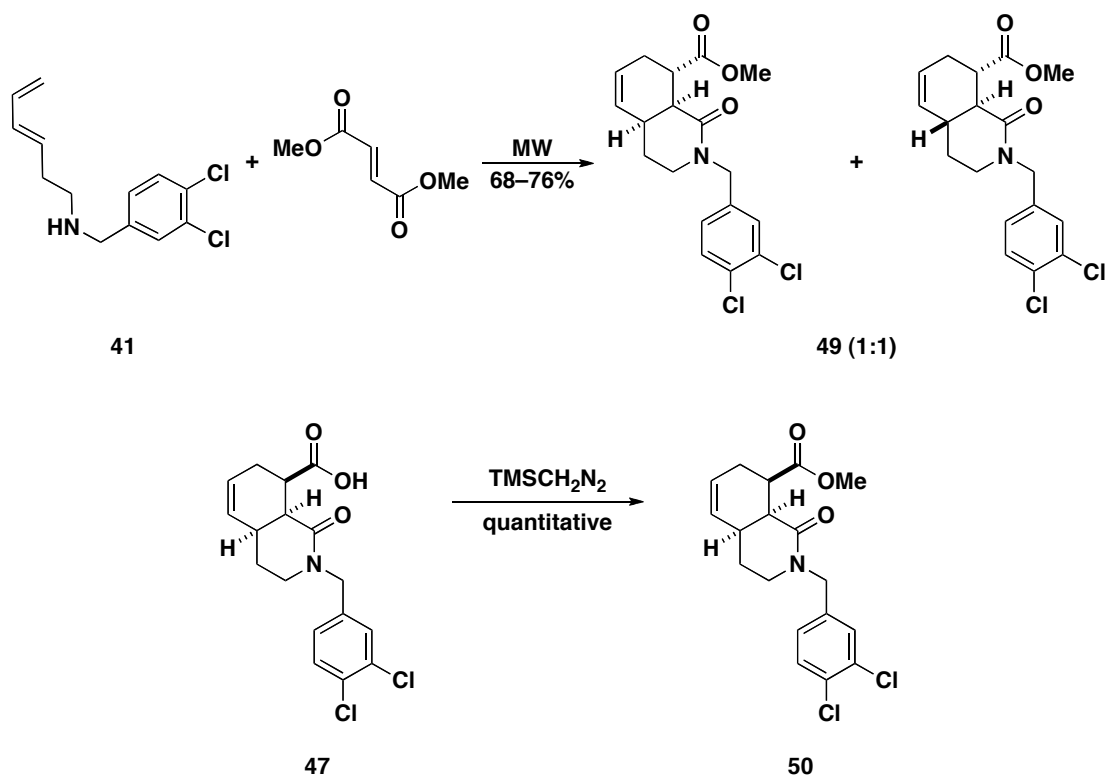
During the course of our studies, we have determined by X-ray crystallographic analysis that the reaction occurs stereospecifically to provide exclusively the *endo* product (Schemes 28 and 29) as predicted by the Alder endo rule.³³ The use of a *trans* dieneophile was briefly examined. The reaction of (*E*)-*N*-(3,4-dichlorobenzyl)hexa-3,5-dien-1-amine (**41**) with dimethyl fumarate produced compound **49** as an inseparable equimolar mixture of isomers in 68–76% combined yield (Scheme 29). Methylation of isoquinolinone **47**, prepared from the reaction of

maleic anhydride with amino diene **41**, using (trimethylsilyl)diazomethane afforded ester **50**. This compound was shown to be isomerically distinct from compound **49** (Scheme 29), proving that these Diels–Alder reactions are both stereospecific.

Scheme 28

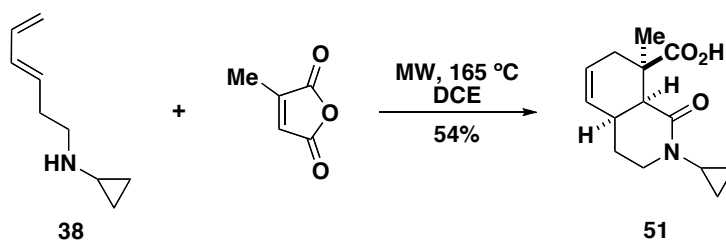


Scheme 29



Determination of dieneophile scope. We then sought to investigate other dieneophiles as partners in the Diels–Alder reaction. In addition to the experiments with dimethyl fumarate, we examined the use of citraconic anhydride and *N*-benzyl maleimide as dieneophiles in the one-pot reaction sequence. In my hands, the reaction of **37** with citraconic anhydride did not proceed to give the desired product. However, it was later shown by Kevin Frankowski that the reaction of the cyclopropyl amino diene **38** with citraconic anhydride under the standard conditions did afford the methyl substituted isoquinolinone product **51** in 54% yield (Scheme 30).

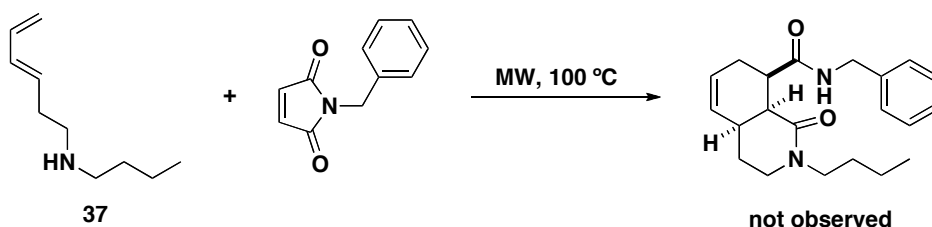
Scheme 30



We envisioned that reaction with a maleimide would allow for direct diversification of the former carboxylic acid site. Direct entry into the amide compounds by employing maleimides would eliminate a coupling step later in the reaction sequence and obviate the purification of the highly polar carboxylic acids. Reaction of (*E*)-*N*-butylhexa-3,5-dien-1-amine (**37**) with *N*-benzyl maleimide in dichloroethane using microwave irradiation under the standard reaction conditions did not provide any of the desired product, and only starting material was observed by

NMR (Scheme 31). Similar results were obtained with a number of additives including ytterbium triflate, boron trifluoride diethyl etherate, dimethyl aluminum chloride, scandium triflate, tin tetrachloride, and titanium tetrachloride.

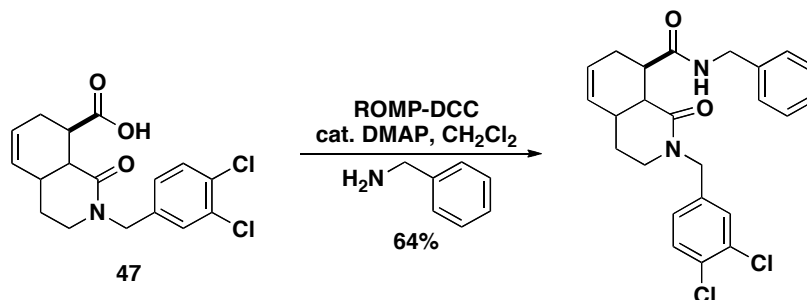
Scheme 31



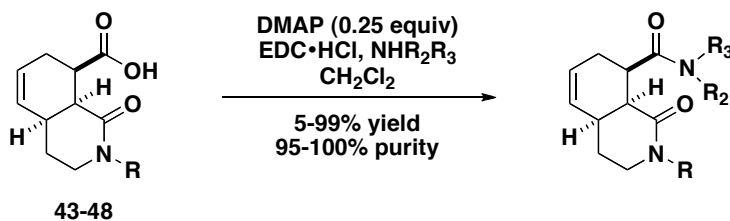
Diversification of the isoquinolinone scaffolds for compound library development. We envisioned several different ways in which we could diversify the isoquinolinone carboxylic acid scaffolds and decided to synthesize a set of amides as an initial approach to library construction (Scheme 32). Initial attempts used a polymeric DCC reagent and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 (Scheme 32 a).³⁴ This approach, developed by Hanson and coworkers, facilitated removal of reaction byproducts upon the addition of ethyl acetate following reaction completion and subsequent filtration of the polymer after it crashes out of solution. Subsequent aqueous extraction to remove the excess amine and DMAP provided the desired amide product in 64% yield.³⁴

Scheme 32

(a)



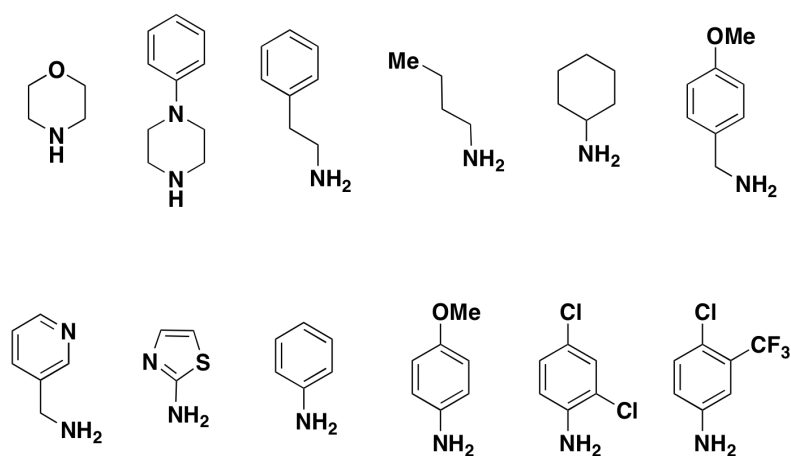
(b)



Ultimately however, we settled on diversifying the acid scaffold using a peptide coupling procedure employing a catalytic amount of DMAP and *N*-(3'-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride ($\text{EDC}\cdot\text{HCl}$) as the primary coupling reagent for library formation (Scheme 32), as this approach was better established, the product yields were overall higher, and compounds were isolated in high purities (>90% in all but 2 cases). In the initial library synthesis, performed by Kevin Frankowski,³⁵ the six scaffolds were reacted with twelve structurally and electronically different amines (Table 5). The reactions were stirred at room temperature for 14 hours then partitioned between CH_2Cl_2 and water in phase

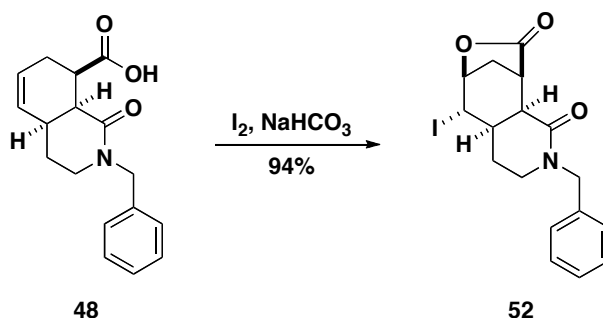
separator tubes fitted with hydrophobic filters. The organic layers obtained were directly subjected to solid phase extraction (SPE). Elution with CH₂Cl₂:acetone (1:1) provided the crude amide-coupled products affording an initial library of 72 compounds for biological screening.

Table 5. Amines for preliminary library synthesis.



We also envisioned that further reaction of the alkene double bond, resulting from the Diels–Alder reaction, with molecular iodine, would allow for an excellent handle to perform lactonization of the acid through an iodolactonization process (Scheme 33). Initial studies by Yibin Zeng that were later confirmed by Kevin Frankowski and myself demonstrated the conversion of isoquinolinone **48** to the iodolactone **53** shown, although this promising tangent has not been further explored.

Scheme 33



Summary. Since the completion of this study, the Diels–Alder/acylation reaction has been further applied to library synthesis, and the compounds from the initial library by Kevin Frankowski have been submitted for biological screening.

This project has allowed us to examine the feasibility of performing a one-pot Diels–Alder/acylation reaction sequence to form octahydroisoquinolinone carboxylic acids by exploiting the reactivity inherent to maleic anhydride. The products contain carboxylic acid and olefin moieties that are amenable to further diversification. Initial compound libraries focused on diversifying the carboxylic acid group via an amide coupling reaction.

In this way, the utility of the Diels–Alder/acylation reaction in preparing biologically interesting heterocycles was demonstrated. The successful development of this method resulted in a scalable synthetic route into the target scaffold that is tolerant of a variety of substitution patterns. Moreover, it led to increased interest in expanding the scope of this reaction sequence to include other heteroatoms, ring sizes and diversification methods for library generation.

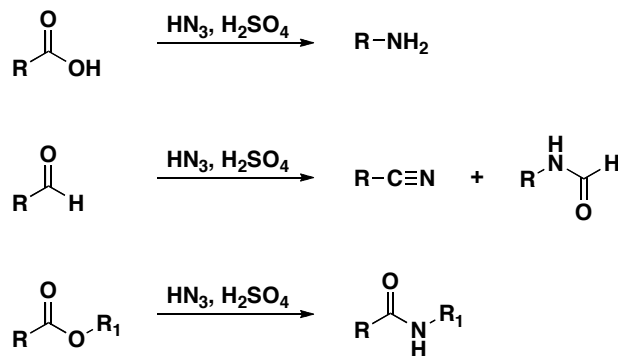
Chapter 3

Development of a first-generation catalytic Schmidt reaction

Introduction. Nitrogen is present in many natural products and medicinally relevant compounds. Thus, a need exists for effective ways to prepare molecules such as amines, amides and lactams. The most successful methods to synthesize compounds containing these types of functional groups utilize simple, readily available starting materials that can be acted upon to yield more complex structures.

The Schmidt reaction of ketones. The protic acid-promoted reactions of hydrazoic acid or alkyl azides with ketones, aldehydes, and carboxylic acids to give amides, nitriles, or amines are referred to as Schmidt reactions (Scheme 34).³⁶⁻⁴³ These reactions produce different products but do have certain features in common.

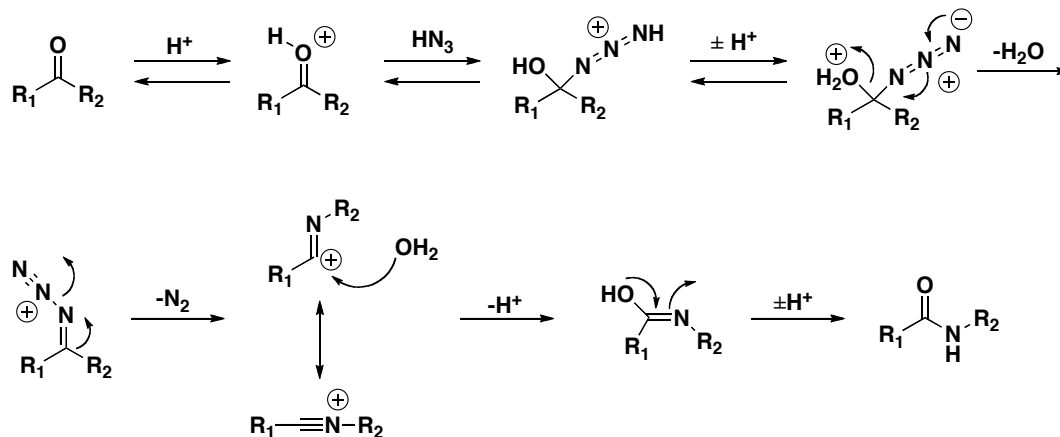
Scheme 34



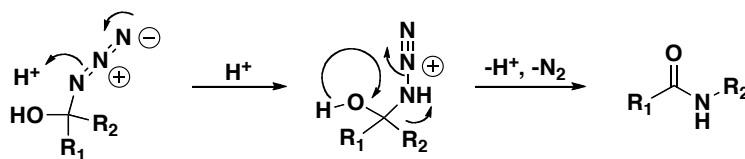
In the classical Schmidt reaction, a ketone is activated towards nucleophilic attack by a protic acid (Scheme 35 a). The addition of hydrazoic acid leads to the formation of an azidohydrin intermediate, which can decompose after protonation of the hydroxyl group and the subsequent loss of water.^{42–44} The resulting imine can then undergo a rearrangement where the R₂ group *trans* to the leaving diazonium group selectively migrates. The *trans* correlation between the migrating group and the leaving group is analogous to that observed in other related rearrangement reactions such as the Beckmann, Hoffman, Lossen and Stieglitz rearrangements.^{45–48} This step generates an iminium carbocation that can be attacked by water; tautomerization finally yields the amide product. Alternatively, another mechanism could be proposed (Scheme 35 b) in which the azidohydrin intermediate undergoes a direct 1, 2-migration of the R₂ group from the central carbon to the proximal nitrogen, releasing N₂. However, most authors think that mechanism (a) is operational for hydrazoic acid.⁴⁹

Scheme 35

(a)



(b)

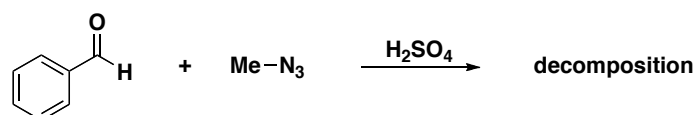


Hydrazoic acid and alkyl azides are closely related. Early investigations into the Schmidt reaction examined the hypothesis that alkyl azides would participate in a similar manner to hydrazoic acid. However, these first attempts to employ alkyl azides in Schmidt reactions were not successful. Papers published in the 1940's by Briggs⁵⁰ and Smith⁵¹ independently reported that the attempted Schmidt reaction of benzaldehyde with methyl azide failed. No nitrogen insertion products were observed during the course of the reaction. Instead, only decomposition of the starting azide was observed (Scheme 36 a). Boyer and coworkers later reported low yields of an

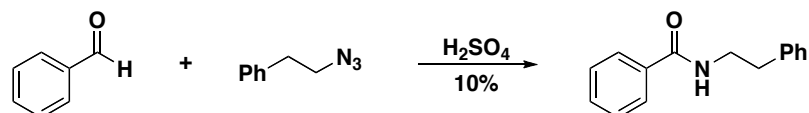
amide product obtained during the reaction of certain alkyl azides with aromatic aldehydes (Scheme 36 b).^{52,53}

Scheme 36

(a)



(b)



It was not until the 1990's that useful variations of the Schmidt reaction were developed employing alkyl azides as reaction substrates. The first synthetically viable Schmidt reactions of alkyl azides and ketones developed were intramolecular. Previous work in Aubé's laboratories has demonstrated that upon treatment with protic or Lewis acids, certain azido-tethered ketones can be converted to the desired lactams quite readily (Table 6).¹²

Table 6. Lactams synthesized using the intramolecular Schmidt reaction.¹²

entry	ketone	lactam	conditions	yield (%)
1			TFA, 25 min	66
2			TFA, 40 min	83
3			TFA, 1 h	93
4			TFA, 3.5 h	85
5			TFA, 3.5 h	87
6			TFA, 15 min	74
7			TfOH, 2 d	45
8			TFA, 1 h	91
9			TFA, 16 h	96

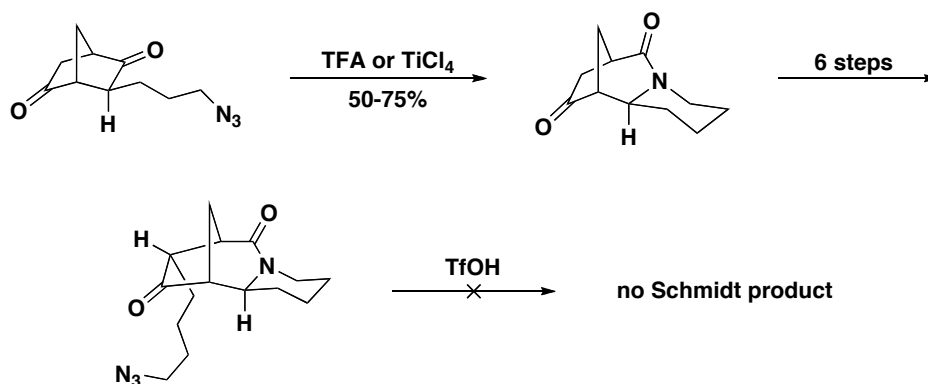
The success of these intramolecular Schmidt reactions was attributed to the supposition that the initial nucleophilic addition step is more facile when compared to the more difficult intermolecular reactions attempted by Briggs,⁵⁰ Smith,⁵¹ and Boyer.^{52,53} As shown in Table 6, the intramolecular substrates our group examined resulted in the desired ring expanded lactams in good to excellent yields when a 3-azidopropyl group was adjacent to the ketone. Shortly after the initial paper describing the intramolecular Schmidt reaction between azides and ketones was published, Pearson and coworkers reported an analogous intramolecular Schmidt reaction between azides and cations.^{12,49,54} The publication of these independent discoveries established that Schmidt reactions of alkyl azides were possible. Intermolecular versions of both reactions were discovered shortly thereafter.^{55,56}

It has been shown that stoichiometric or superstoichiometric amounts of TFA or TiCl_4 are necessary for a successful Schmidt reaction.^{12,57} The necessity for a full equivalent of Lewis or protic acid stems from the greater Lewis basicity of the amide product when compared to the ketone starting material. Thus, the reaction promoter is bound up due to chelation with the more basic lactam product, causing product inhibition.⁵⁸ The use of such significant amounts of Lewis or protic acids also affects which substrates are amenable to the intramolecular Schmidt reaction. Currently the reaction works on a variety of ketones and aldehydes with tether lengths of three and four carbons, which are not acid sensitive.

In work done towards the asymmetric synthesis of (+)-sparteine, John Wendt attempted to perform a double Schmidt reaction as the key step in his synthetic route

to this important natural product (Scheme 37).⁵⁹ The first of the two Schmidt reactions did occur. However, numerous attempts towards the second Schmidt reaction were unsuccessful. This could be due to product inhibition by the lactam resulting from the first Schmidt reaction, thereby preventing the second reaction from occurring. However, the use of excess Lewis acid was also unsuccessful, suggesting that chelation of the Lewis acid to the first lactam could slow down the second Schmidt reaction by preventing activation of the remaining ketone. It was during this work that development of a catalytic Schmidt reaction was first envisioned.

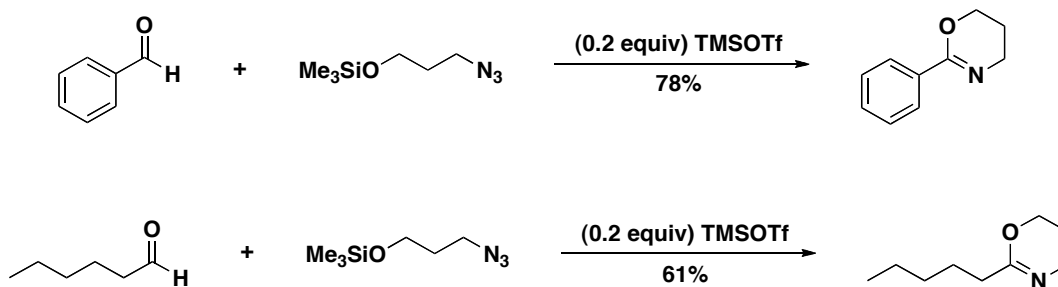
Scheme 37



The use of catalysts to promote an analogous Schmidt reaction between ketones and hydroxyalkyl azides was previously examined in this research group. Thus, Jennifer Badiang demonstrated that the reaction of a tethered azide with a ketone could be accomplished using catalytic amounts of TMSOTf to afford the

desired the oxazine and oxazoline heterocycles in 78% and 61% yields, respectively (Scheme 38).⁶⁰

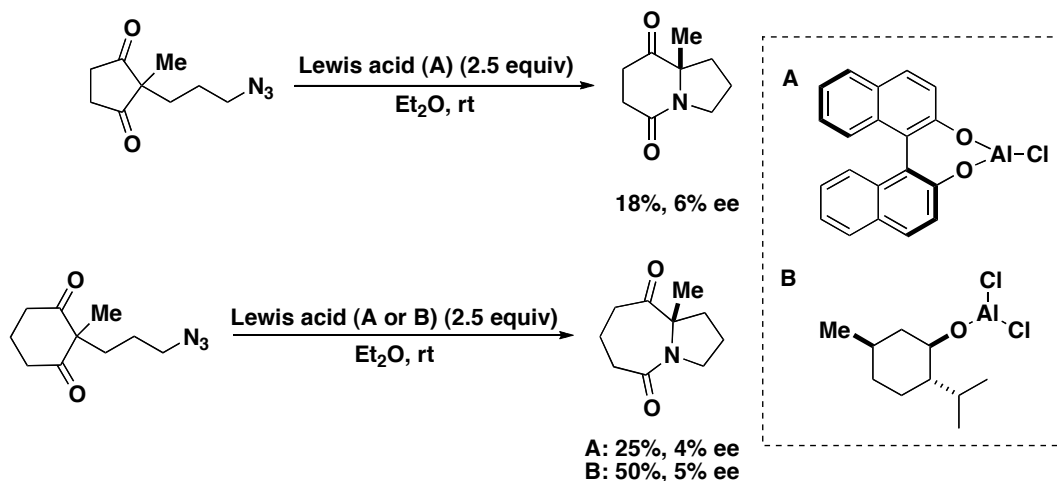
Scheme 38



In addition to developing a catalytic Schmidt reaction, this group has been seeking to develop an asymmetric variant of the Schmidt reaction. The only example of an asymmetric Schmidt process reported in the literature was published by the Marsden laboratory in 2006.⁶¹ With limited success in this paper, the work towards desymmetrization of prochiral azido diketones is described. They found that the intramolecular Schmidt reaction could be promoted with 2.5 equivalents of an aluminum-based Lewis acid. Under these conditions the reaction proceeded with complete regioselectivity. However, attempts towards an asymmetric induction by the incorporation of chiral ligands (such as (*S*)-BINOL or (–)-menthol) into the promoters were unsuccessful (Scheme 39). The yields of these transformations were modest at best and incomplete conversion was observed in all cases. This paper highlights the difficulty in developing an asymmetric Schmidt reaction, though the potential of such a transformation is considerable. Work in this laboratory is focused on the

development of new applications for this reaction, including catalytic and asymmetric variations.

Scheme 39

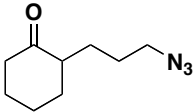
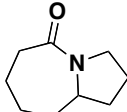


Initial studies towards a catalytic Schmidt reaction. The development of a catalytic Schmidt reaction could be the first step towards further study into a useful catalytic asymmetric variant of the Schmidt reaction, and provide a route to other interesting heterocycles currently unavailable using the standard Schmidt conditions.

Our efforts toward a catalytic Schmidt reaction began with a Lewis acid survey for the conversion of azidoketone **53** to bicyclic lactam **54** done by Sze Wan Li.¹² She investigated various conditions for accomplishing the reaction (Table 7). However, all but one of the reaction conditions examined in the initial study led to incomplete conversion or no reaction as determined by NMR. A variety of catalysts,

catalyst loadings, additives, solvents and temperatures were examined with little success.

Table 7. Initial survey of conditions for a catalytic Schmidt reaction.^a

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>53</p> </div> <div style="margin: 0 20px;"> <p>conditions</p> <p>→</p> </div> <div style="text-align: center;">  <p>54</p> </div> </div>		
entry	conditions	conversion(%) ^b
1	5 mol % CuSO ₄ •H ₂ O, H ₂ O, 180 °C, 4 h	37
2	5 mol % CuSO ₄ •H ₂ O, THF, 120 °C, 4 h	NR
3	5 mol % CuBr, NEt ₃ , H ₂ O/CH ₃ CN, rt, 12 h	NR
4	5 mol % CuSO ₄ , 50 mol % C ₆ H ₇ NaO ₆ , H ₂ O, 180 °C, 4 h	23
5	10 mol % Sc(OTf) ₃ , H ₃ CCN, 80 °C, 16 h	47
6	5 mol % Sc(OTf) ₃ , <i>t</i> -BuOH, 140 °C, 4 h	26
7	5 mol % Sc(OTf) ₃ , THF/H ₂ O, 180 °C, 4 h	59
8	5 mol % Sc(OTf) ₃ , 160 °C, 4 h	80
9	5 mol % Sc(OTf) ₃ , DCE, rt then 2 h at 200 °C	17
10	25 mol % TiCl ₄ , CH ₂ Cl ₂ , rt	NR
11	10 mol % Sc(OTf) ₃ , CH ₂ Cl ₂ , 20 mol % DBU	9
12	25 mol % TFA, DCM, rt, 18 h	NR
13	50 mol % Sc(OTf) ₃ , H ₂ O 180 °C 4 h	>95

^a Sze Wan Li; ^b Determined by ¹H NMR.

The only reaction that demonstrated high conversion employed 50 mol % of the lanthanide Lewis acid, scandium triflate in water. In this reaction, complete conversion of the azidoketone **53** to the desired ring expanded bicyclic lactam **54** was observed after four hours of microwave irradiation at 180 °C. The lactam **54** was isolated in 57% yield. However, the reaction was unsuccessful when tried on another known Schmidt substrate.¹² From this one promising result, began our studies towards the development of a catalytic Schmidt reaction.

Synthesis of the necessary azidoketone Schmidt precursors. To perform the necessary experiments, the test substrate, 2-(3'-azidopropyl)cyclohexanone (**53**) was prepared for this study as previously reported.¹²

Six other azidoketones were synthesized for this study using published precedent.¹² Beginning with commercially available cyclic ketones, entry into six different four to seven-membered ring alkylated ketones was quickly established (Figure 3). Several of the compounds synthesized were new and would provide novel bicyclic lactams generated from the catalytic Schmidt reaction if successful. New compounds prepared as part of this methodology study include 2-(3'-azidopropyl)-cyclobutanone (**55**), 2-(3'-azidopropyl)-4-methylcyclohexanone (**58**), and 2-(3'-azidopropyl)-4-phenylcyclohexanone (**59**).

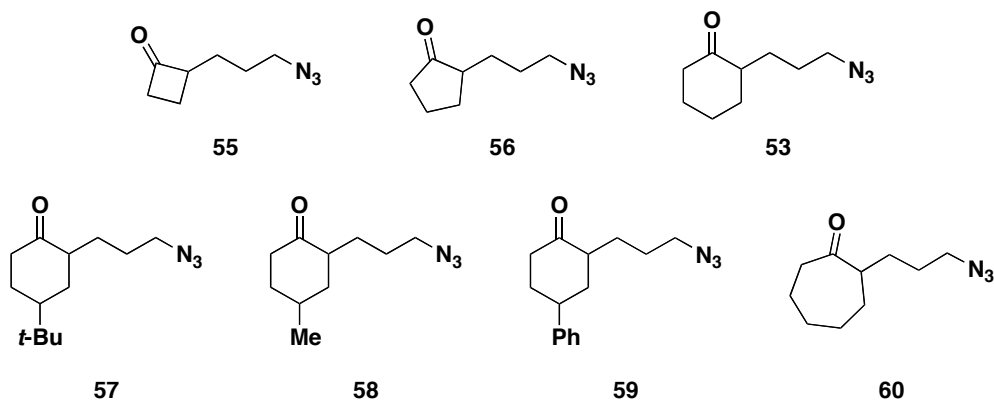


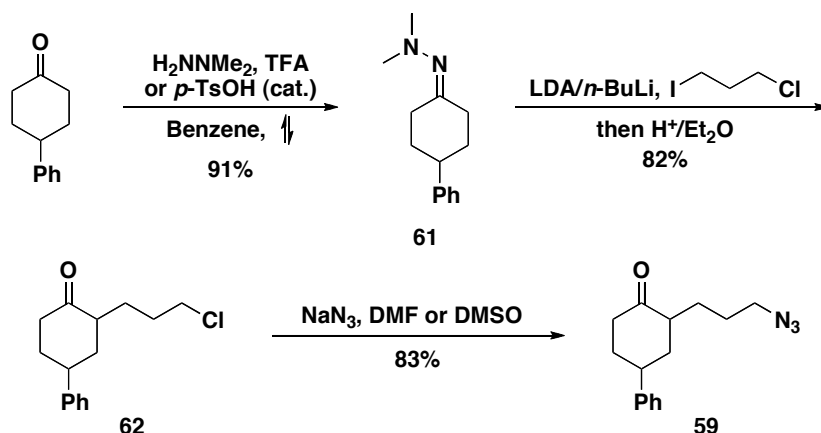
Figure 3. 2-(3'-azidopropyl)ketones prepared for study in this methodology.

A typical experiment employing 4-phenylcyclohexanone proceeded as follows. Commercially available 4-phenylcyclohexanone was converted to the corresponding hydrazone **61** via a condensation reaction with excess *N,N*-dimethylhydrazine, in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate or trifluoroacetic acid, in refluxing benzene for several hours or overnight. Once collection of the calculated amount of water into the Dean–Stark trap was completed, the reaction was worked up. Subsequent recrystallization from hexanes and ethyl acetate afforded 1,1-dimethyl-2-(4'-phenylcyclohexylidene)hydrazone (**61**) in 91% yield (Scheme 40).

Hydrazone **61** was then alkylated with 1-chloro-3-iodopropane. Addition of the hydrazone to a solution of lithium diisopropyl amide or *n*-butyl lithium in THF at 0 °C led to the formation of the hydrazone anion. Subsequent addition of the alkylating reagent, followed by acid hydrolysis of the hydrazone gave the alkylated ketone **62** in 82% after chromatographic purification. Finally, azide displacement of

the chloride was accomplished by an S_N2 reaction with excess NaN₃ in DMF or DMSO to provide the desired alkyl azide **59** in good overall yield starting from 4-phenyl cyclohexanone (Scheme 40).

Scheme 40



We similarly synthesized both 2-(3'-azidopropyl)-cyclobutanone (**55**), and 2-(3'-azidopropyl)-4-methylcyclohexanone (**58**), proceeding through the known hydrazones of cyclobutanone⁶² and 4-methylcyclohexanone.⁶³ Alkylation with 1-chloro-3-iodopropane led to the new 2-(3'-chloropropyl)-cyclobutanone (**63**) and 2-(3'-chloropropyl)-4-methylcyclohexanone (**64**) in yields of 56% and 84%, respectively. Subsequent azide displacement afforded the azidoketones **55** and **58** in 87% and 88% yield, respectively.

Eight other alkyl azide substrates prepared for this methodology were also synthesized (Figure 4). These included two azido- β -keto esters, ethyl 1-(3'-azidopropyl)-2-oxocyclohexanecarboxylate (**65**), and methyl 1-(3'-azidopropyl)-2-

oxocyclopentanecarboxylate (**66**), synthesized according to a published procedure, and were each obtained in 70% over both steps (Scheme 41).¹²

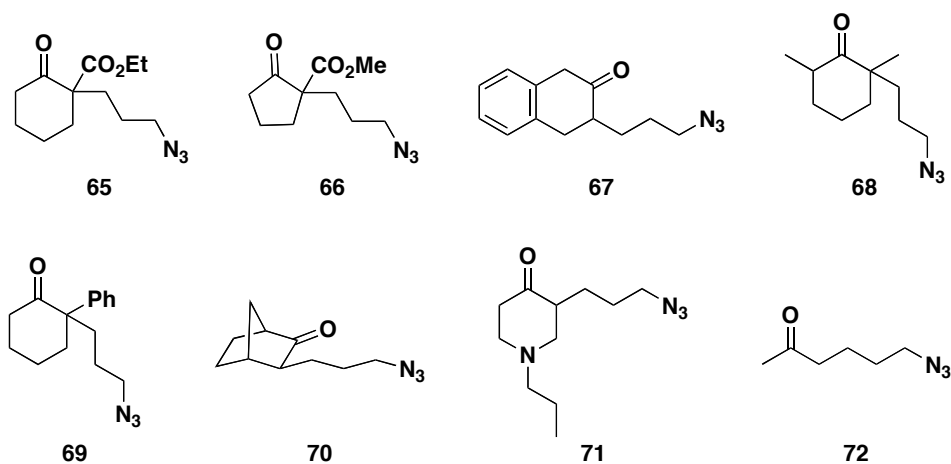
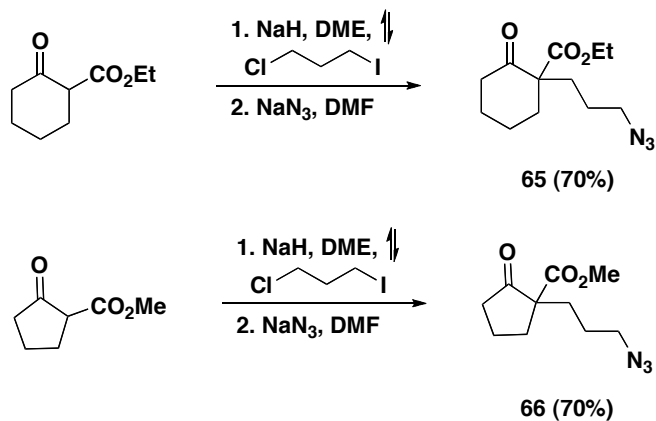


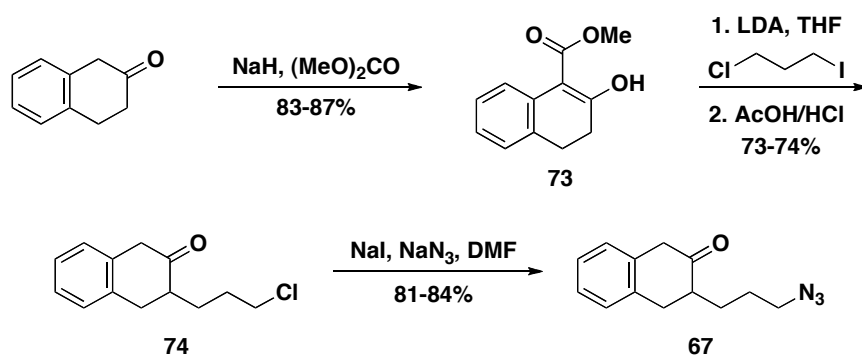
Figure 4. Other 3-azidopropyl ketones prepared for methodology exploration.

Scheme 41



3-(3'-Azidopropyl)-3,4-dihydronaphthalen-2(1H)-one (**67**) was synthesized in three steps from the commercially available β -tetralone using a published procedure (Scheme 42).⁶⁴

Scheme 42



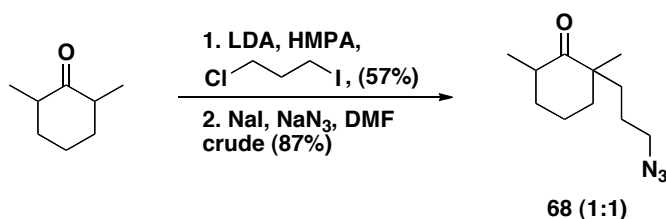
To examine substitution effects, 2-(3'-azidopropyl)-2,6-dimethylcyclohexanone (**68**) and 2-(3'-azidopropyl)-2-phenylcyclohexanone (**69**) were also prepared (Scheme 43).^{65,66} The 2,6-dimethylcyclohexanone-containing azide was synthesized by first forming the enolate via treatment with LDA (Scheme 43 a).⁶⁵ Alkylation was then carried out with 1-chloro-3-iodopropane. 2-(3'-Chloropropyl)-2,6-dimethylcyclohexanone (**75**) was isolated as a 1:1 mixture of inseparable diastereomers. Subsequent azide displacement was accomplished via treatment with in situ formed alkyl iodide. Addition of water and work up yielded a mixture of inseparable diastereomeric azides **68** that was significantly contaminated with diastereomeric olefins resulting from terminal chloride elimination. The mixture

of azides was used as isolated (as previously reported) in the ensuing Schmidt reaction as it was chromatographically inseparable from the elimination byproducts.

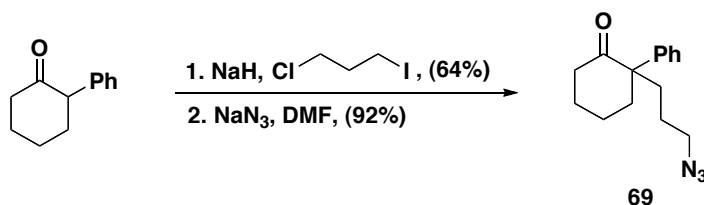
The synthesis of 2-(3'-azidopropyl)-2-phenylcyclohexanone (**69**) proceeded through generation of the enolate as previously reported,⁶⁶ with the addition of NaH and 1-chloro-3-iodopropane, and afforded 2-(3'-chloropropyl)-2-phenylcyclohexanone (**76**) in 64% yield (Scheme 43 b). Subsequent azide displacement in DMF afforded the 2-(3'-azidopropyl)-2-phenylcyclohexanone (**69**) in 92% after chromatography.

Scheme 43

(a)



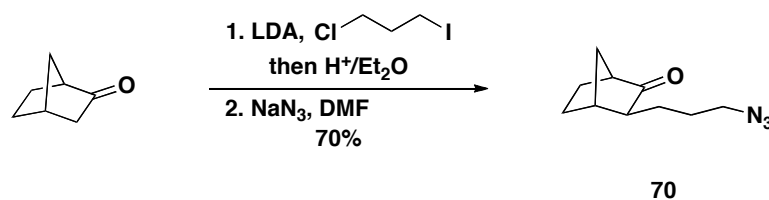
(b)



A similar substrate to that utilized in studies towards the total synthesis of sparteine⁵⁹ was also prepared. For this experiment, commercially available

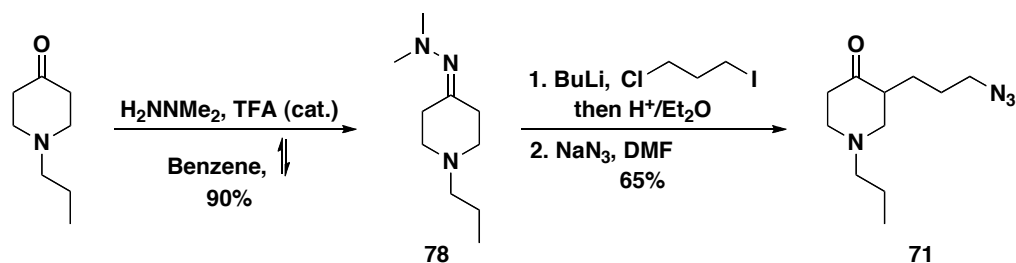
norcamphor was alkylated with 1-chloro-3-iodopropane to provide (1*S**,3*S**,4*R**)-3-(3'-chloropropyl)bicyclo[2.2.1]heptan-2-one (**77**) in 78% yield (Scheme 44). Subsequent azide displacement afforded (1*S**,3*S**,4*R**)-3-(3'-azidopropyl)bicyclo[2.2.1]heptan-2-one (**70**) in 90% yield. Azidoketone **70** differed from Wendt's substrate by one less carbon in the appended side chain.

Scheme 44



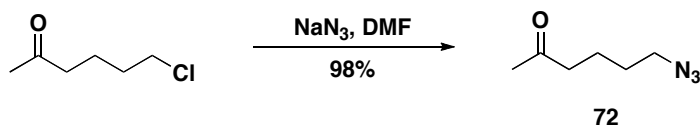
To determine the effect of increased polarity and basic nitrogen on the Schmidt reaction, 3-(3'-azidopropyl)-1-propylpiperidin-4-one (**71**) was prepared. Using a procedure reported by Fleming and coworkers, *N*-propyl piperidone was converted to the known hydrazone **78** in 90% yield (Scheme 45).⁶⁷ 4-(2',2'-dimethylhydrazono)-1-propylpiperidine (**78**) was then alkylated with 1-chloro-3-iodopropane using a method similar to that previously described to give 3-(3'-chloropropyl)-1-propylpiperidin-4-one (**79**) in 77% yield. Azide displacement of alkylated piperidone **79** occurred cleanly to give **71** in 84% yield using the standard conditions.

Scheme 45



Finally, we sought to examine an acyclic azidoketone within the context of this reaction (Scheme 46). Thus, commercially available 6-chloro-2-hexanone was subjected to azide displacement and afforded the known 6-azido-2-hexanone (**72**) in 98% yield.¹²

Scheme 46



Development of conditions for a catalytic Schmidt reaction. Having in hand a range of azidoketones, we began to screen conditions for promoting the desired catalytic reaction. Encouraged by the single positive result previously achieved by Sze Wan Li, the test substrate **53** was screened against various Lewis acids, solvents, reaction times and temperatures. We carefully set up our screens, changing one variable at a time while keeping the rest of the conditions constant.

Initially, reactions were heated to 180–190 °C for 4 hours in an oil bath. We

set up our first experiments by decreasing the catalyst loading to 25 mol %. A typical experiment with azido ketone **53** was performed in the following manner. To a small pressure tube was added 0.41 mmol of the azido ketone **53** and 0.75 mL of water. This was followed by addition of the catalyst and another 0.75 mL of water, and then placed in the oil bath to stir. We noted that the azide was insoluble in water, giving a biphasic mixture. The resulting reaction had a clear, brownish appearance. Extraction with CH₂Cl₂ and subsequent workup afforded a brown oil. NMR analysis of the crude reaction mixture showed complete conversion to the product. The purified lactam **54** was furnished as a pale yellow oil in 71% yield after chromatography.

Further reaction screening with 2-(3'-azidopropyl)cyclohexanone (**53**) determined that the catalyst loading could be lowered to 10 mol % with complete conversion still observed. The lactam **54** could be cleanly isolated from this experiment in a similar 73% yield. Decreasing the catalyst loading to 5 mol % gave ca. 50% conversion after 4 hours. In our search for appropriate conditions other solvents and Lewis acids were examined; the results from these experiments are shown in Table 8. Acetonitrile, toluene, mixtures of water with dichloroethane, alcoholic solvents, and methylene chloride were all examined for their ability to promote the reaction. The solvent study showed incomplete conversion in the reaction for all solvents examined except water.

Table 8. Lewis acid and solvent survey.

entry	conditions	concentration [M]	conversion (%) ^a	yield (%)
1	25 mol % Sc(OTf) ₃ , H ₂ O 180 °C, 4 h	0.26	>95	77 ^a , 71 ^b
2	10 mol % Sc(OTf) ₃ , H ₂ O 180 °C, 4 h	0.27	>95	83 ^a , 73 ^b
3	5 mol % Sc(OTf) ₃ , H ₂ O 180 °C, 4 h	0.24	50 (50% SM)	--
4	25 mol % Sc(OTf) ₃ , toluene 180–200 °C, 4 h	0.16	<20	--
5	25 mol % Sc(OTf) ₃ , H ₃ CCN 180 °C, 4 h	0.20	<10	--
6	25 mol % LiClO ₄ , toluene 180 °C, 4 h	0.33	<20	--
7	25 mol % LiClO ₄ , H ₂ O 180 °C, 4 h	0.22	<20	--
8	25 mol % AuCl, H ₂ O 180 °C, 4 h	0.17	>95	41 ^a

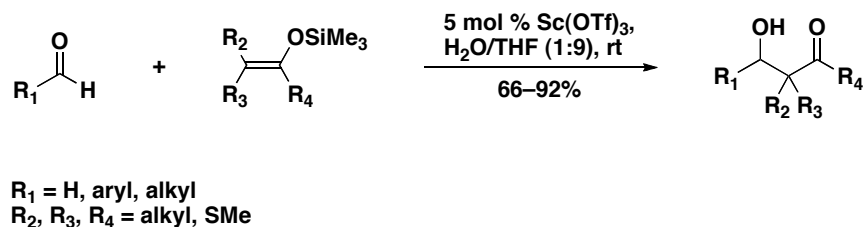
^a Determined by ¹H NMR^b isolated yield

We subsequently began to examine the ability of other Lewis acids to promote this reaction. Neither copper sulfate (CuSO₄) nor lithium perchlorate (LiClO₄) in toluene and water (to reach the higher temperatures used in the reaction previously), catalyzed appreciable conversion of the azide to product as determined by NMR analysis. Gold (I) chloride (AuCl) was then examined in this reaction. Upon disappearance of **53** (ca. 4 hours), the reaction mixture was cooled and worked up. Complete conversion of **53** to the desired lactam **54** was observed via NMR of the

crude reaction mixture. However, only a 41% yield of the product was determined by NMR analysis (Table 8).

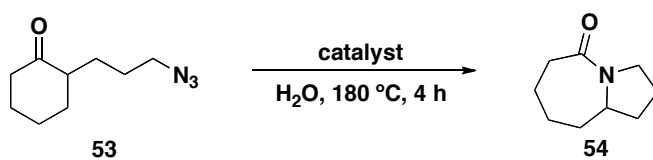
In other work, Kobayashi and coworkers have demonstrated that lanthanide Lewis acids catalyze the Mukaiyama aldol reaction (Scheme 47).⁶⁸ In this vein, we decided to examine other lanthanide triflates. Additionally, chiral versions of ytterbium and scandium Lewis acids are known, and success here might translate to the development of a stereoselective Schmidt reaction.

Scheme 47



As demonstrated in Table 9, a variety of commercially available lanthanide triflates were investigated, but all experiments resulted in incomplete conversion of the azide substrate to the ring-expanded lactam. These results demonstrate that scandium triflate is the preferred Lewis acid for carrying out the desired transformation.

Table 9. Lanthanide Lewis-acid survey.

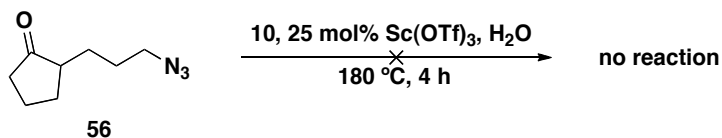


53 catalyst 54
 H_2O , 180 °C, 4 h

entry	catalyst	conversion (%) ^a
1	25 mol % Yb(OTf) ₃	46
2	25 mol % Eu(OTf) ₃	<10
3	25 mol % Er(OTf) ₃	<20
4	25 mol % Ho(OTf) ₃	26
5	25 mol % Gd(OTf) ₃	<15
6	25 mol % Nd(OTf) ₃	28
7	25 mol % Dy(OTf) ₃	37
8	25 mol % Pr(OTf) ₃	<20
9	25 mol % Sc(OTf) ₃	>95

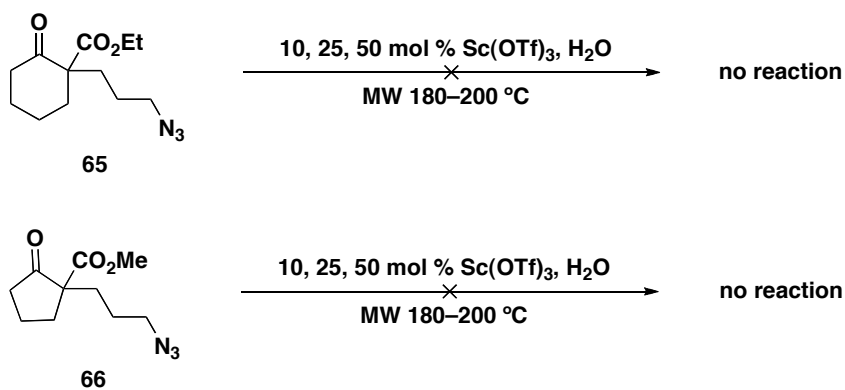
Application of other azidoketones in this reaction sequence. The application of scandium triflate conditions to 2-(3'-azidopropyl)cyclopentanone (**56**) was examined. The azide was reacted with 10 mol % scandium triflate in water for 4 hours at 180 °C (Scheme 48). Monitoring the reaction by TLC analysis showed no conversion to product. The catalyst loading was increased to 25 mol % and still no conversion to product was indicated by TLC and NMR analysis of the crude reaction.

Scheme 48



We then examined two β -keto ester substrates, 2-carboethoxy-2-(3'-azidopropyl)cyclohexanone (**65**) and 2-carbomethoxy-2-(3'-azidopropyl)cyclopentanone (**66**) (Scheme 49). Both of these substrates work well under the standard Schmidt reaction conditions with either TFA or TiCl_4 , giving the desired products in yields of 93%, and 66%, respectively. However, when subjected to our scandium triflate catalysis in water, no conversion to product was observed using oil-bath heating. Various catalyst loadings and reaction times were examined, but no conversion was seen at $180\text{ }^\circ\text{C}$. Instead, starting material and some degradation products were observed. Therefore, the azidoketones **65** and **66** were not recovered from the reaction.

Scheme 49



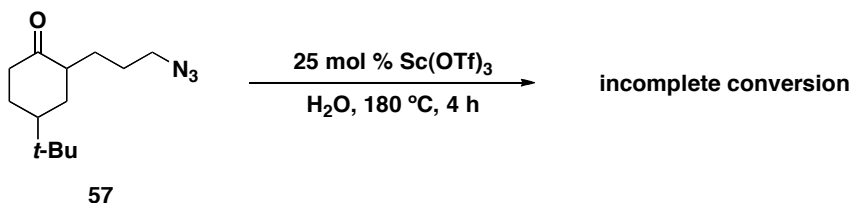
The use of microwave irradiation in the Schmidt reaction. Microwave irradiation uses electromagnetic irradiation as a method for heating reactions within a pressurized cavity. Two types of microwaves are available for chemistry purposes, mono-mode and multi-mode microwaves. Mono-mode microwaves are equipped to send a single microwave through a glass vial. This mode of irradiation provides improved temperature control by directing the electromagnetic irradiation through a small cavity with a wave detector onto the reaction vial, which is set at a fixed distance from the wave source.⁶⁹ In this type of heating only one vessel can be heated at a time. Multi-mode microwave cavities are conceptually similar to a household microwave oven. In this case, the microwaves enter and are reflected by the walls and the load over the typically large cavity, in a chaotic manner. A stirrer ensures that the field distribution is as uniform as possible in these types of reactors. In this type of microwave, there is the ability to heat multiple vessels at the same time. Thus, the two types of microwaves used in chemistry are quite different.

For these experiments, a mono-mode microwave irradiation source was selected. The single wave provides increased reproducibility for each single reaction via a more controlled source of microwave irradiation. Furthermore, in the initial experiments the Schmidt reaction was not performed on a large scale that would necessitate the use of a multi-mode instrument.

The first substrate subjected to our reaction conditions utilizing microwave irradiation was 2-(3'-azidopropyl)-4-*tert*-butylcyclohexanone (**57**). A typical experiment was set up in a microwave vial in the same manner as for the oil bath reactions, then heated in the microwave for four hours utilizing fixed hold time (meaning the microwave does not start counting time until the desired temperature is

reached). Upon completion of the reaction time, TLC analysis indicated incomplete conversion (ca. 50%).

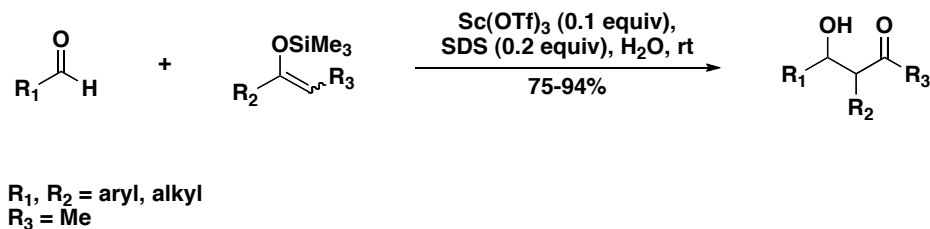
Scheme 50



This result was disappointing after the success with 2-(3'-azidopropyl)cyclohexanone (**53**). We subsequently began to investigate methods to promote this reaction on substrates besides **53**. We hypothesized that the insolubility of the azide in water might affect the progress of the reaction. 2-(3'-azidopropyl)cyclohexanone (**53**) is less hydrophobic than 2-(3'-azidopropyl)-4-*tert*-butylcyclohexanone (**57**), likely increasing its ability to interact with the water-soluble Sc(OTf)₃ catalyst.

Research from Kobayashi and coworkers demonstrated that the Mukaiyama aldol reaction in water often occurs as a biphasic mixture when promoted by Sc(OTf)₃ (Scheme 51).⁷⁰ In this work, they demonstrated that the use of a detergent or phase transfer reagent improves the reaction yields and is often a key to its success.

Scheme 51

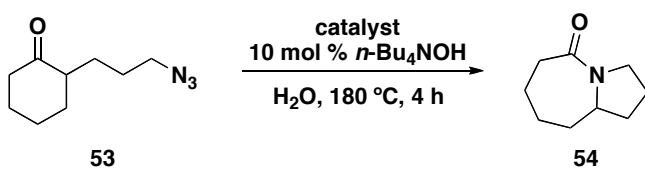


Following this example, we examined the reaction of 2-(3'-azidopropyl)-4-*tert*-butylcyclohexanone (**57**) with the addition of phase transfer reagents tetrabutyl ammonium hydroxide and tetrabutyl ammonium chloride. To our delight, the addition of 10 mol % of either reagent facilitated complete conversion of **57** into its corresponding lactam **80** after 4 hours at 180 °C. Lactam **80** was isolated from this reaction in 50% yield.

On the basis of these results, the lanthanide Lewis acid survey was repeated, this time utilizing 10 mol % tetrabutyl ammonium hydroxide or chloride. It was determined that both phase transfer reagents promoted the reaction. Our findings are summarized in Table 10. These data were consistent with previous findings that determined scandium triflate to be the most efficient lanthanide triflate available for promoting the catalytic Schmidt reaction. In all other experiments incomplete conversion to product was observed.

Additionally, two protic acids were examined for their ability to promote the catalytic Schmidt reaction. However, neither *p*-toluenesulfonic acid (27 mol %) nor hydrochloric acid (38 mol %) promoted the reaction to an appreciable extent under these conditions.

Table 10. Lanthanide Lewis acid survey with phase transfer catalyst.

<div><div></div><div>5354</div></div>		
entry	catalyst	conversion (%) ^a
1	25 mol % Ho(OTf) ₃	31
2	25 mol % Gd(OTf) ₃	12
3	25 mol % Pr(OTf) ₃	20
4	25 mol % Er(OTf) ₃	36
5	25 mol % Eu(OTf) ₃	<10
6	25 mol % Nd(OTf) ₃	24
7	25 mol % Yb(OTf) ₃	38
8	25 mol % Sc(OTf) ₃	>95
9	38 mol % HCl	<10
10	27 mol % <i>p</i> -TsOH	<5

^a Determined by ¹H NMR.

Next we began to explore the scope of the reaction using previously described azidoketones. Our investigations into the substrate scope of this reaction began with 2-(3'-azidopropyl)cyclopentanone (**56**). Experiments were set up as previously described. Lower reaction temperatures were found to lead to incomplete or no conversion and longer reaction times. Workup of the reaction was accomplished by performing multiple extractions with methylene chloride to remove the more polar

lactam product from the water, followed by several washes of the organic extracts with brine to remove phase transfer catalyst. Chromatography removed any residual phase transfer reagent, and afforded the desired lactam **81** in 54% yield.

NMR analysis was used to determine conversion to the desired lactam product prior to purification. Typically, only clean products were observed in these experiments (Table 11). Only in two cases (entries 7 and 8) were incomplete conversions observed. Our investigations subsequently continued with several 4-substituted cyclohexanones.

Table 11. Results from the catalytic Schmidt reaction.

entry	n	R	conditions	conversion (%) ^a	yield (%)	lactam (#)
1	0	H	25 mol% Sc(OTf) ₃	>95	60	82
2	1	H	25 mol% Sc(OTf) ₃ , 10 mol% <i>n</i> -Bu ₄ NOH	>95	54	83, 64 ^e
3	2	H	10 mol% Sc(OTf) ₃	>95	73	85 ^e
4	2	<i>t</i> -Bu	25 mol% Sc(OTf) ₃ , 10 mol% <i>n</i> -Bu ₄ NOH	>95	50	92 ^e
5	2	Me	25 mol% Sc(OTf) ₃ , 10 mol% <i>n</i> -Bu ₄ NOH	>95	59	83
6	2	Ph	25 mol% Sc(OTf) ₃ , 10 mol% <i>n</i> -Bu ₄ NOH	>95	55	84
7	β-tetralone		25 mol% Sc(OTf) ₃ , 10 mol% <i>n</i> -Bu ₄ NOH	~85	45 ^b	85
8	3	H	25 mol% Sc(OTf) ₃ , 10 mol% <i>n</i> -Bu ₄ NOH	60	31 ^b	86
9	2	H	No Lewis acid, 10 mol% <i>n</i> -Bu ₄ NOH	<5	0	--
10	2	H	No Lewis acid, No <i>n</i> -Bu ₄ NOH	<5	0	--

^aNMR conversion; ^bDetermined by ¹H NMR; ^cNovel Schmidt substrate, 2-methylcyclobutanone used previously.¹² Reported yield: 66%; ^dNovel Schmidt substrate; ^eReference 12.

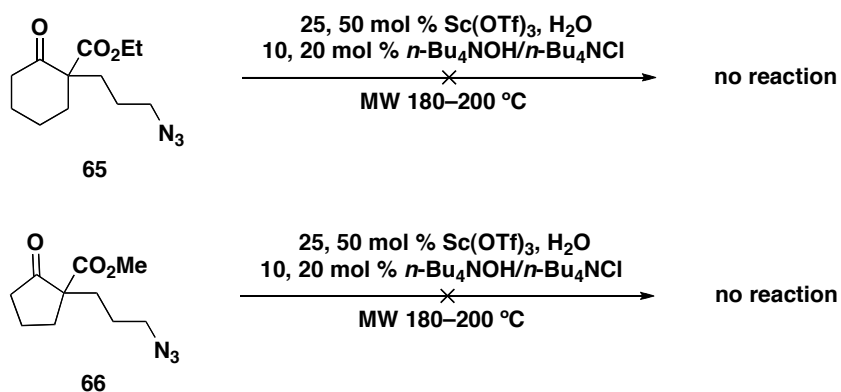
We determined that substitution at the 4-position was tolerated under the reaction conditions to provide the lactam products. 2-(3'-Azidopropyl)-4-methylcyclohexanone (**58**) afforded a ca. 3:1 inseparable mixture of two diastereomeric ring expanded lactams **83** from this reaction in 59% yield. Subsequently, 2-(3'-azidopropyl)-4-phenylcyclohexanone (**59**) under the same conditions led to the isolation of a ca. 4:1 inseparable mixture of two diastereomeric lactams **84** in 55% yield. In contrast, the 4-phenyl substituted azide **59** and chloride **62** precursors were separable by preparatory TLC. The azide diastereomers were identified by their ¹³C NMR spectra. The C-4 methine carbon in the *trans* diastereomer appeared at 37.4 and is upfield of the corresponding carbon in the *cis* diastereomer at 43.5, as expected for the isomer bearing an axial substituent at C-2. However, all attempts to purify useful quantities of **59** and **62** were unsuccessful. Therefore, the Schmidt reaction was carried out on the mixture. Other substitution distal to the azide tether should be tolerated; though, examples of this were not examined due to the increasing complexity of the resulting mixtures of diastereomeric lactam products.

As part of our studies into the scope of this reaction, cyclic azidoketones of varying ring sizes were investigated including 2-(3'-azidopropyl)cyclobutanone (**55**), 2-(3'-azidopropyl)cyclopentanone (**56**), and 2-(3'-azidopropyl)cycloheptanone (**60**). In most cases, complete conversion of the starting material was observed with moderate to good yields (33-60%) of the resulting bicyclic lactams **54**, **81**, **82**, and **86**.

The early stage development of this methodology has demonstrated some important limitations that warrant further investigation for the general applicability of

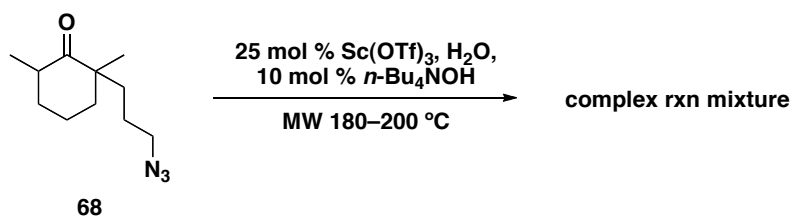
the reaction. Currently, this methodology does not tolerate substituents alpha to the ketone, unlike the traditional intramolecular Schmidt reaction. For example, the two azido- β -keto ester substrates (**65** and **66**) did not participate in the catalytic Schmidt reaction. Various conditions were examined in order to promote the reaction. These included varying the catalyst loading to 25 and 50 mol %, increasing the reaction times, as well as the addition of 10 and 20 mol % of tetrabutyl ammonium hydroxide or tetrabutyl ammonium chloride as phase transfer reagents. However, no conversion to the desired product was observed. The reaction was further pushed to 200 °C in the microwave at a measured pressure of 18 mbar, but only starting material and degradation products were observed by NMR analysis after 4-6 hours at this temperature (Scheme 52).

Scheme 52



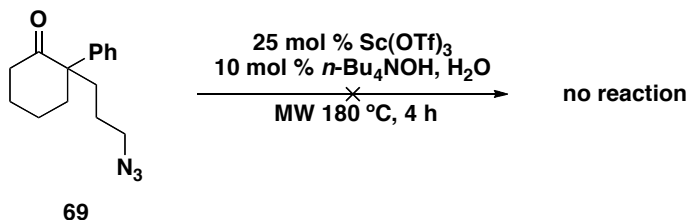
The 2,6-dimethyl substrate **68**, which Wroblewski⁶⁵ had shown to participate in the Schmidt reaction, gave only trace conversion to product as observed in the crude NMR upon workup (Scheme 53).

Scheme 53



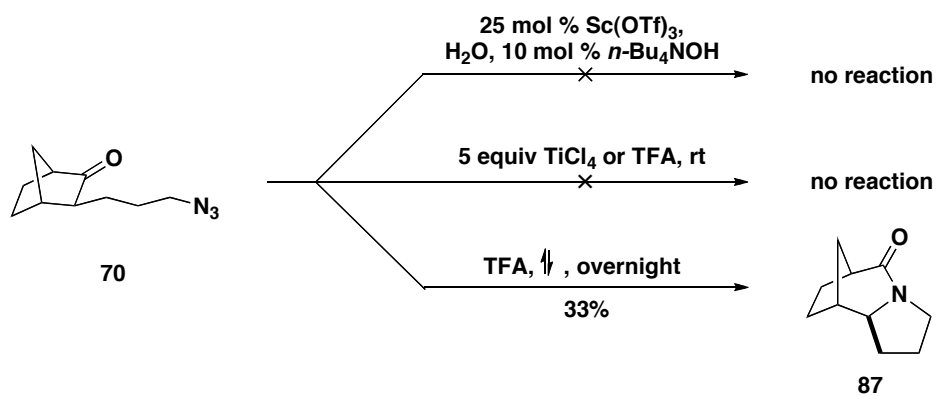
The 2-phenylcyclohexanone azide (**69**),⁶⁶ known to participate in the intermolecular Schmidt reaction, was also subjected to the catalytic variant (Scheme 54). NMR analysis of the crude reaction material indicated only the presence of starting material with no degradation observed. The starting material could be recovered in quantitative yield from the unsuccessful reaction.

Scheme 54



(1*S**,3*S**,4*R**)-3-(3'-azidopropyl)bicyclo[2.2.1]heptan-2-one (**70**), a compound similar to those for sparteine alkaloid synthesis,⁵⁹ was subjected to the catalytic Schmidt reaction, which resulted solely in the recovery of starting material (Scheme 55). Further investigation of increased catalyst loadings or increased reaction times was unsuccessful, and the starting material was recovered in >75% in all cases. This was not surprising since we determined that this substrate did not participate in a traditional intramolecular Schmidt reaction using five equivalents of titanium tetrachloride from 0 °C to room temperature or neat trifluoroacetic acid at room temperature. A modest conversion was only observed when azide **70** was subjected to refluxing trifluoroacetic acid for 12–18 hours. These conditions afforded lactam **87** in 33% yield.

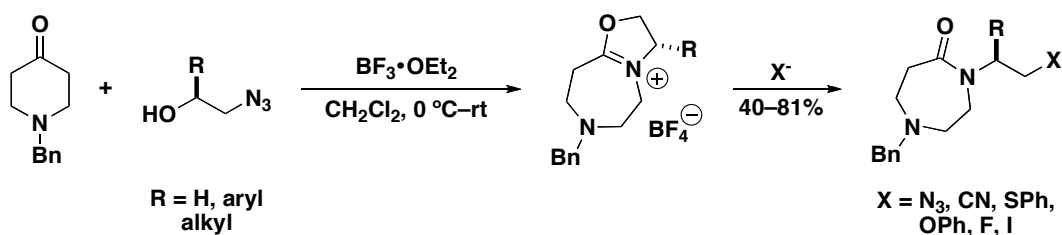
Scheme 55



Polar compounds, such as piperidones, were also envisioned as potential substrates for the catalytic variant of the Schmidt reaction occurring in water. We

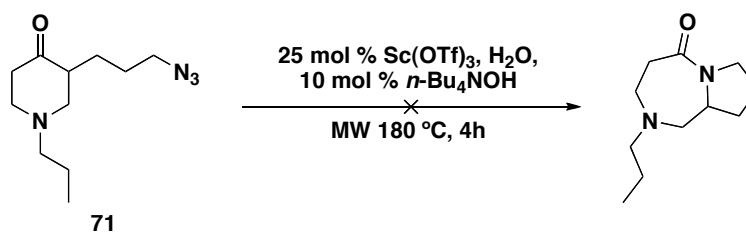
hypothesized that these substrates would have increased solubility over the standard Schmidt substrates and might readily participate in the reaction. Substrates of this type are known to undergo intermolecular reactions with hydroxyalkyl azides as demonstrated in previous work from this laboratory (Scheme 56).^{71,72} However, these types of substrates were not studied in the original investigations of the intramolecular Schmidt reaction, even though they would provide entry into interesting fused bicyclic diazapinone ring systems.

Scheme 56



Thus **71**, 3-(3'-azidopropyl)-1-propylpiperidin-4-one described earlier, was subjected to the reaction conditions (Scheme 57). To our disappointment, none of the desired ring expanded product was observed and the reaction resulted solely in degradation as indicated by NMR analysis. Additionally, this substrate did not participate in the intramolecular Schmidt reaction when treated with an excess of titanium tetrachloride; only degradation was observed.

Scheme 57

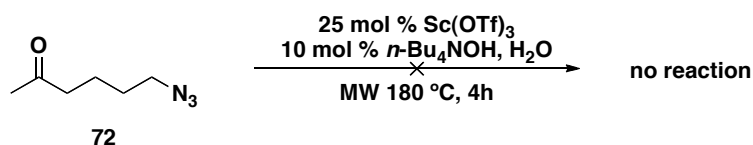


We had not yet examined acyclic azidoketones as part of this methodology. Previously, Mossman and Milligan^{12b} reported the intramolecular Schmidt reaction of 6-azido-2-hexanone and other acyclic azidoketones (Table 12). The lactam arising from azide **72** was isolated in 75% yield. Next, we examined 6-azido-2-hexanone (**72**) as a representative acyclic substrate in this catalytic version of the intermolecular Schmidt reaction. Unfortunately, the reaction did not proceed and no conversion to the desired lactam product was detected (Scheme 58).

Table 12. Acyclic substrates from the standard Schmidt reaction.^{12b}

entry	n	R ₁	Lewis acid	Yield (%)
1	1	Me	TFA	--
2	1	PhCH ₂	TFA or TiCl ₄	--
3	2	Me	TFA	75
4	2	MeO ₂ CCH ₂	TFA	69
5	2	Ph	TFA	77

Scheme 58



Summary. This work has demonstrated that a catalytic Schmidt reaction is possible. Presently, the best general conditions for performing the desired transformation employ 25 mol % of scandium triflate as the Lewis acid promoter, 10 mol% of tetra-*n*-butyl ammonium hydroxide or tetra-*n*-butyl ammonium chloride as a phase transfer catalyst, and water as the preferred reaction solvent. Microwave irradiation to heat the reaction mixtures for 4 hours at 180 °C affords the desired ring-expanded lactam products in moderate to good yields.

These conditions can be considered “greener” than those currently employed in the intramolecular Schmidt reaction. We have eliminated the use of halogenated solvents, which are hazardous and costly to remediate and dispose of. Utilization of a catalytic amount of Lewis acid, typically 25 mol % of scandium triflate, is a significant decrease from 2.5–5 equivalents of trifluoroacetic acid or titanium tetrachloride. As an added benefit scandium triflate is an air stable solid, and thus is easier to handle and use. Inclusion of a phase transfer reagent, such as tetra-*n*-butyl ammonium hydroxide or tetra-*n*-butyl ammonium chloride, allowed for increased solubility of the keto azide in the water layer and assisted in formation of the Schmidt product in cases where the reaction did not take place with catalyst and solvent alone.

Further investigation into a second-generation variant of this reaction would entail the careful examination of other additives to increase azide solubility in water, and assist with catalyst turnover. Kobayashi and coworkers have found success with the use of sodium dodecyl sulfate (SDS) as a detergent in their $\text{Sc}(\text{OTf})_3$ catalyzed aqueous Mukaiyama aldol reactions.⁷⁰ Moreover, the substrates that showed no reaction or degradation during this study should be further screened utilizing different reaction conditions (e.g. different additives, solvent mixtures, catalysts) to determine their level of participation in a catalytic transformation. Furthermore, preliminary observations support that neat conditions are particularly effective for the catalytic intermolecular Schmidt reaction.

This catalytic Schmidt variation has potential to broaden the scope of the current intramolecular version by allowing participation of more acid sensitive substrates. Finally, additional work into the development of this method will provide a benchmark towards the development of a highly desirable stereoselective variant of the intramolecular Schmidt reaction.

Chapter 4

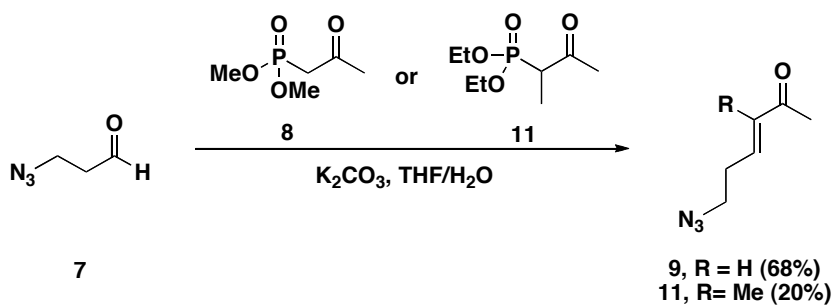
Experimental Section

General procedures. ^1H and ^{13}C NMR spectra were collected on a Bruker DRX-400 (400 MHz and 100 MHz, respectively) or a Bruker AM-500 (500 MHz and 125 MHz, respectively) instrument. Unless otherwise noted, all samples were dissolved in CDCl_3 and the shifts expressed in parts per million (δ) relative to residual CHCl_3 as an internal standard. ^{13}C NMR multiplicities were determined with the aid of an APT pulse sequence, differentiating the signals for methyl and methine carbons as “d” from methylene and quaternary carbons as “u”. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; qd, quartet of doublets; td, triplet of doublets. The infrared (IR) spectra were recorded on Perkin-Elmer 1420 spectrometer or a Perkin-Elmer Spectrum One FT-IR and the absorption frequencies are reported in cm^{-1} . Melting points were determined on an Electrothermal Mel-Temp model number 101D apparatus and are uncorrected. All flash chromatography was performed using Sorbent technologies silica gel (32-63 mesh) with the reported eluent system. The chromatography solvent “wet ether” refers to the organic layer of a 9:1:0.1 ether:aqueous potassium phosphate, monobasic (0.5 M):glacial acetic acid mixture.³⁰ Methylene chloride and THF were dried by passing through two packed columns of neutral alumina using the PurSolv solvent purification system (Innovative Technology Inc.) prior to use. All chemicals were used as purchased from commercial suppliers. Dry flasks (noted) were flame dried

under vacuum and then placed under a positive pressure of argon. Microwave vials (noted) were purchased from commercial suppliers (Biotage part numbers: 355458 (0.2-0.5 mL), 352016 (0.5-2mL), 351521 (2-5 mL), 354833 (10-20 mL)). Mono-mode microwave used was a Biotage Initiator instrument. Fixed hold time is a microwave parameter in which time is not counted until the reaction reaches the desired temperature.

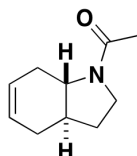
Chapter 1: Experimental Procedures

General Information. Azido enones **9** and **12** were prepared via a Horner–Wadsworth–Emmons condensation of the known 3-azido propionaldehyde **6**⁷³ and the corresponding β -keto phosphonate **8**.⁷⁴ *Caution! All low molecular weight alkyl azides are potential explosion hazards and should be used with appropriate caution.*



(E)-6-Azido-3-hexen-2-one (9). To a solution of β -keto phosphonate **8**⁷⁴ (1.60 g, 10 mmol) in THF/ H_2O (4:1, 40 mL) was added K_2CO_3 (2.10 g, 15 mmol). The resulting solution was cooled in an ice bath followed by dropwise addition of the 3-azido propionaldehyde **7** (1.0 g, 10 mmol) in THF (4 mL). The mixture was stirred in an ice bath for 1 h and then quenched with saturated aqueous $NaHCO_3$. The reaction mixture was partitioned between water and EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give an oil. Chromatography (10% EtOAc/hexane) afforded 940 mg (68%) of **9** as an oil. R_f = 0.46 (25% EtOAc/hexane); 1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.51 (m, 2H), 3.44 (t, J

= 6.7 Hz, 2H), 6.15 (d, J = 16.0 Hz, 1H), 6.74 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 27.5, 32.2, 50.0, 133.6, 143.4, 198.5; IR (neat) 1709, 1644 cm^{-1} ; HRMS calcd for $\text{C}_6\text{H}_{10}\text{N}_3\text{O}$: 140.0824, found 140.0853.

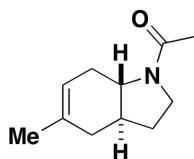


(±)-*Trans*(3a, 7a)-1-acetyl-2,3,3a,4,7,7a-hexahydro-1H-indole (21).

Butadiene was bubbled through a solution of enone **9** (200 mg, 1.4 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 5 min followed by dropwise addition of MeAlCl_2 (1.0 M in hexanes), 4.3 mL). The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 26 h. After dilution with CH_2Cl_2 (100 mL), aqueous NaHCO_3 was added. The organic layer was separated, washed with brine, and dried (MgSO_4). The organic layer was filtered, and concentrated to give 128 mg (54%) of **21**, a yellow oil, as a ca. 2.5:1 mixture of rotamers. R_f = 0.5 (EtOAc). IR (neat) 1633 cm^{-1} ; HRMS calcd for $\text{C}_{10}\text{H}_{16}\text{NO}$: 166.1232, found 166.1221. Major rotamer: ^1H NMR (400 MHz, CDCl_3) δ 1.46-1.49 (m, 2H), 1.89-1.95 (m, 1H), 1.99 (s, 3H), 2.27-2.28 (m, 2H), 3.14-3.18 (m, 2H), 3.51 (t, J = 9.4 Hz, 1H), 5.60 (s, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 23.7, 30.5, 31.0, 33.0, 42.4, 48.9, 60.6, 126.5, 170.7. Minor rotamer: ^1H NMR (400 MHz, CDCl_3) (diagnostic peaks only) δ 2.01 (s), 3.36-3.43 (m), 3.83-3.88 (d, J = 8.2, 11.8 Hz); ^{13}C NMR (100.6 MHz, CDCl_3) δ 23.4, 29.2, 34.2, 44.1, 47.8, 125.3, 127.9, 170.8.

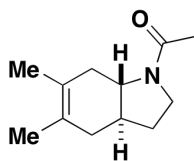
General procedure for the Diels–Alder/Schmidt reaction using enone **9.**

To a solution of azido enone **9** (0.4–2.1 mmol) and diene (3 equiv) in CH₂Cl₂ (15–20 mL) at 0 °C was added AlMeCl₂ (3 equiv). The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 12 h, and then quenched with aqueous NaHCO₃. The mixture was partitioned between water and CHCl₃. The organic layer was collected, dried (Na₂SO₄), filtered, and concentrated to give an oil. Chromatography (10% EtOAc/hexane followed by 1–2% MeOH/CHCl₃) afforded the desired lactams.



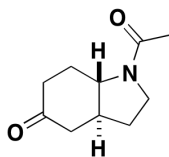
(±)-Trans(3a, 7a)-1-acetyl-5-methyl-2,3,3a,4,7,7a-hexahydro-1H-indole

(22). Enone **9** (292 mg, 2.1 mmol) afforded 275 mg (73%) of **22**, a yellow oil, as a ca. 2.2:1 mixture of rotamers. R_f = 0.25 (EtOAc). IR (neat) 1650 cm⁻¹; HRMS calcd for C₁₁H₁₇NO: 180.1388, found 180.1385. Major rotamer: ¹H NMR (400 MHz, CDCl₃) δ 1.62 (s, 3H), 1.73–1.95 (m, 5H), 2.06–2.11 (m, 2H), 3.42 (dt, J = 6.21, 17.1 Hz, 2H), 3.52 (t, J = 9.6 Hz, 1H), 5.29 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 23.6, 23.7, 30.4, 32.5, 35.7, 43.0, 49.2, 60.8, 121.0, 133.9, 170.7. Minor rotamer (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 1.65 (s), 2.00 (s), 3.24 (dt, J = 5.7, 17.7 Hz), 3.86 (dd, J = 8.2, 11.8 Hz); ¹³C NMR (100.6 MHz, CDCl₃) δ 23.3, 23.6, 29.2, 33.8, 35.8, 44.6, 48.1, 60.6, 119.4, 135.5, 170.8.



(±)-1-*Trans*(3a, 7a)-acetyl-5,6-dimethyl-2,3,3a4,7,7a-hexahydro-1*H*-indole

(23). Enone **9** (200 mg, 1.4 mmol) afforded 208 mg (75%) of **23**, a yellow oil, as a ca. 2.4:1 mixture of rotamers. R_f = 0.28 (EtOAc). IR (neat) 1650 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{20}\text{NO}$: 194.1545, found 194.1551. Major rotamer: ^1H NMR (400 MHz, CDCl_3) δ 1.58 (s, 3H), 1.85-1.97 (m, 5H), 1.99 (s, 3H), 2.07-2.11 (m, 2H), 3.42 (dt, J = 6.3, 17.4 Hz, 1H), 3.52 (t, J = 9.9 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 19.4, 19.7, 23.7, 29.7, 36.9, 38.8, 43.1, 49.2, 61.2, 125.3, 125.8, 170.7. Minor rotamer (diagnostic peaks only) ^1H NMR (400 MHz, CDCl_3) δ 1.61 (s), 2.03 (s); ^{13}C NMR (100.6 MHz, CDCl_3) δ 19.9, 23.4, 29.2, 37.0, 40.1, 44.7, 48.1, 61.0, 124.2, 126.9, 170.8.



(±)-1-*Trans*(3a, 7a)-acetyl-octahydro-1*H*-indol-5-one (24).

Enone **9** (275 mg, 2.0 mmol) afforded 220 mg (71%) of **24**, a yellow oil, as a ca. 1.4:1 mixture of rotamers. R_f = 0.18 (EtOAc). IR (neat) 1712 cm^{-1} ; HRMS calcd for $\text{C}_{10}\text{H}_{16}\text{NO}_2$: 182.1181, found 182.1161. Major rotamer: ^1H NMR (400 MHz, CDCl_3) δ 1.31-1.45 (m, 2H), 1.91 (s, 3H), 2.19-2.34 (m, 3H), 2.46 (m, 1H), 3.28-3.45 (m, 1H) 3.39-3.46 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 23.6, 28.9, 30.2, 39.4, 45.3, 45.5, 49.3,

62.3, 171.3, 209.4. Minor rotamer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.49-1.57 (m), 1.89 (s), 2.50 (m), 3.00-3.06 (m), 3.51-3.56 (m); ^{13}C NMR (100.6 MHz, CDCl_3) δ 23.3, 29.2, 30.4, 39.0, 45.2, 47.1, 48.8, 62.0, 170.9, 208.1.

Chapter 2: Experimental Procedures

List of Known Compounds

The following amino dienes and intermediates are known: (*E*)-ethyl hepta-4,6-dienoate (**2**),^{15,26,27} (*E*)-hexa-3,5-dien-1-ol (**3**),^{15,26,27} (*E*)-hexa-3,5-dienyl methanesulfonate (**4**),¹⁵ (*E*)-6-azidohexa-1,3-diene (**5**),¹⁵ (*E*)-6-bromohexa-1,3-diene (**32**),¹⁵ (*E*)-*N*-benzylhexa-3,5-dien-1-amine (**40**).¹⁵

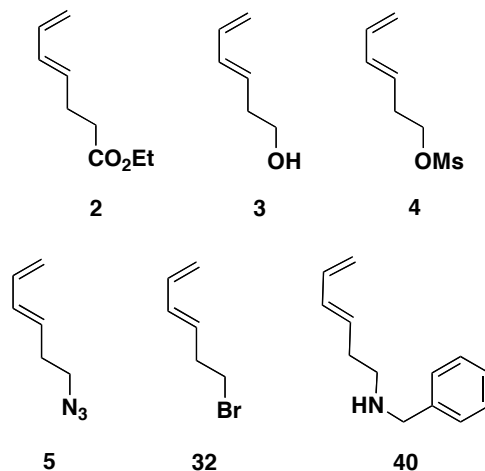
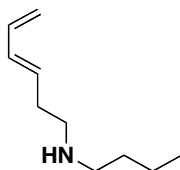
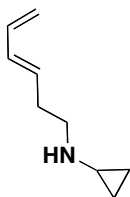


Figure 5. Known dienes.

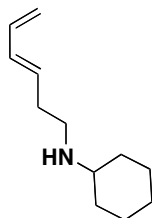


***N*-Butyl-*N*-[(*E*)-3,5-hexadien-1-yl]amine (37).** (*E*)-3,5-Hexadien-1-yl methanesulfonate¹⁵ (727 mg, 4.54 mmol) and *n*-butylamine (4.5 mL, 40 mmol) were stirred in a sealed tube for 19 h at 65 °C. The reaction was partitioned between aqueous NaOH (1 N, 30 mL) and ether. The organic layer was dried (Na₂SO₄), the solvent removed in vacuo and the residue purified by silica chromatography to give **37** as a pale yellow oil (552 mg, 79% yield). *R*_f = 0.25 (CH₂Cl₂/acetone 1:1); ¹H NMR δ 0.92 (t, *J* = 7.3 Hz, 3 H), 1.34 (m, 2 H), 1.47 (m, 2 H), 2.30 (m, 2 H), 2.60 (t, *J* = 7.0 Hz, 2 H), 2.68 (t, *J* = 7.6 Hz, 2 H), 4.98 (d, *J* = 10.0 Hz, 1 H), 5.11 (d, *J* = 16.9 Hz, 1 H), 5.68 (m, 1 H), 6.09-6.15 (m, 1 H), 6.27-6.36 (m, 1 H); ¹³C NMR δ 14.0, 132.6, 132.6, 137.0; u 20.5, 32.3, 33.2, 49.2, 49.7, 115.4; IR 3253, 3086, 1652 cm⁻¹; HRMS calcd for C₁₀H₂₀N: 154.1596, found 154.1571.

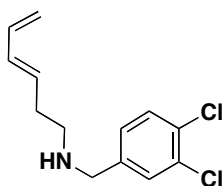


***N*-Cyclopropyl-*N*-[(*E*)-3,5-hexadien-1-yl]amine (38).** (*E*)-3,5-Hexadien-1-yl methanesulfonate¹⁵ (515 mg, 3.22 mmol) and cyclopropylamine (2.2 mL, 32 mmol) were stirred in a sealed tube for 19 h at 65 °C. The reaction was partitioned between aqueous NaOH (1 N, 30 mL) and ether. The organic layer was dried (Na₂SO₄), the

solvent removed in vacuo, and the residue purified by silica chromatography to give **38** as a pale yellow oil (175 mg, 40% yield). $R_f = 0.40$ ($\text{CH}_2\text{Cl}_2/\text{acetone}$ 1:1); ^1H NMR δ 0.29-0.33 (m, 2 H), 0.39–0.43 (m, 2 H), 2.07-2.12 (m, 1 H), 2.24-2.30 (m, 2 H), 2.75 (t, $J = 6.9$ Hz, 2 H), 4.97 (d, $J = 10.0$ Hz, 1 H), 5.09 (d, $J = 16.9$ Hz, 1 H), 5.62-5.69 (m, 1 H), 6.07-6.13 (m, 1 H), 6.25-6.34 (m, 1 H); ^{13}C NMR δ d 30.2, 132.7, 132.7 137.2; u 6.4, 33.2, 48.9, 115.5; IR 3087, 3008, 1652, 1603 cm^{-1} ; HRMS calcd for $\text{C}_{10}\text{H}_{20}\text{N}$: 138.1283, found 138.1244.

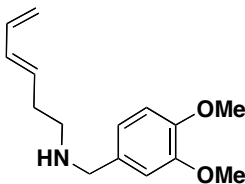


***N*-Cyclohexyl-*N*-[(*E*)-3,5-hexadien-1-yl]amine (39).** (*E*)-3,5-Hexadien-1-yl methanesulfonate¹⁵ (801 mg, 5.00 mmol) and cyclohexylamine (5.7 mL, 50 mmol) were stirred in a sealed tube for 19 h at 65 °C. The reaction was partitioned between aqueous NaOH (1 N, 30 mL) and ether. The organic layer was dried (Na_2SO_4), the solvent removed in vacuo, and the residue purified by silica chromatography to give **39** as a pale yellow oil (734 mg, 4.10 mmol, 82% yield). $R_f = 0.15$ ($\text{CH}_2\text{Cl}_2/\text{acetone}$ 1:1); ^1H NMR δ 1.00-1.26 (m, 6 H), 1.58-1.88 (m, 4 H), 2.24-2.30 (m, 2 H), 2.38-2.43 (m, 1 H), 2.69 (t, $J = 7.0$ Hz, 2 H), 4.97 (d, $J = 10.0$ Hz, 1 H), 5.11 (d, $J = 16.4$ Hz, 1 H), 5.62-5.71 (m, 1 H), 6.07-6.15 (m, 1 H), 6.25-6.36 (m, 1 H); ^{13}C NMR δ d 56.9, 132.7, 132.8, 137.2; u 25.2, 26.3, 33.6, 33.8, 46.3, 115.5; IR 3085, 2927, 1652 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{22}\text{N}$: 180.1752, found 180.1741.



***N*-(3',4'-Dichlorobenzyl)-*N*-[(*E*)-3,5-hexadien-1-yl]amine (41).** (*E*)-3,5-

Hexadien-1-yl methanesulfonate¹⁵ (310 mg, 1.94 mmol) and 3,4-dichlorobenzylamine (1.02 g, 5.81 mmol) and MeCN (1 mL) were stirred in a sealed tube for 1 h at 130 °C under microwave irradiation. The reaction was partitioned between aqueous NaOH (1 N, 30 mL) and ether. The organic layer was dried (Na₂SO₄), the solvent removed in vacuo, and the residue purified by silica chromatography to give **41** as a colorless oil (303 mg, 61% yield). *R*_f = 0.85 (CH₂Cl₂/acetone 1:1); ¹H NMR δ 2.30 (m, 2 H), 2.68 (t, *J* = 6.5 Hz, 2 H), 3.74 (s, 2 H), 5.00 (d, *J* = 8.6 Hz, 1 H), 5.12 (d, *J* = 18.4 Hz, 1 H), 5.63-5.70 (m, 1 H), 6.08-6.15 (m, 1 H), 6.26-6.36 (m, 1 H), 7.15 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.38 (d, *J* = 8.2 Hz, 1 H), 7.43 (d, *J* = 1.7 Hz, 1 H); ¹³C NMR δ d 127.4, 130.0, 130.3, 132.2, 132.9, 136.9; u 33.1, 48.5, 52.7, 115.7, 130.7, 132.4, 140.8; IR 3313, 2914, 1651 cm⁻¹; HRMS calcd for C₁₃H₁₆Cl₂N: 256.0660, found 256.0655.

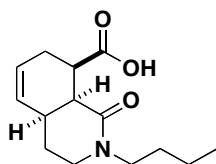


***N*-(3,4-Dimethoxybenzyl)-*N*-[(*E*)-3,5-hexadien-1-yl]amine (42).** (*E*)-3,5-

Hexadien-1-yl methanesulfonate¹⁵ (688 mg, 4.29 mmol) and 3,4-dichlorobenzylamine (2.51 mg, 15.03 mmol) and MeCN (2 mL) were stirred in a sealed tube for 1 h at 130

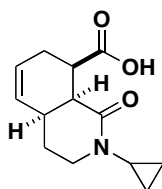
°C under microwave irradiation. The reaction was partitioned between aqueous NaOH (1 N, 30 mL) and ether. The organic layer was dried (Na₂SO₄), the solvent removed in vacuo, and the residue purified by silica chromatography to give **42** as a light yellow oil (686 mg, 65% yield). *R_f* = 0.34 (CH₂Cl₂/acetone 1:1); ¹H NMR δ 2.32 (m, 2 H), 2.72 (t, *J* = 7.1 Hz, 2 H), 3.75 (s, 2 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 5.00 (d, *J* = 10.1 Hz, 1 H), 5.12 (d, *J* = 17.0 Hz, 1 H), 5.65-5.73 (m, 1 H), 6.09-6.16 (m, 1 H), 6.27-6.36 (m, 1 H), 6.81-6.86 (m, 2 H), 6.89 (d, *J* = 1.44 Hz, 1 H); ¹³C NMR δ 56.0, 56.1, 111.1, 111.5, 120.3, 132.7, 132.8, 137.1; u 33.2, 48.7, 53.8, 115.6, 133.2, 148.1, 149.1; IR 2833, 1651 cm⁻¹; HRMS calcd for C₁₅H₂₂NO₂: 248.1651, found 248.1655.

General procedure for the tandem Diels-Alder/acylation reaction of 2-*N*-Butyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (43**).**

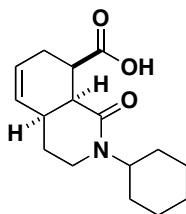


Amino diene **37** (192 mg, 1.25 mmol) and maleic anhydride (153 mg, 1.56 mmol) were dissolved in dichloroethane (3 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue chromatographed to give **43** as a colorless oil (232 mg, 74% yield). The product precipitated as a tan solid upon trituration with hexanes. *R_f* = 0.45 (“wet ether”); mp

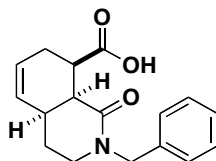
96.5-101.5 °C; ^1H NMR δ 0.93 (t, J = 7.4 Hz, 3 H), 1.29 (q, J = 7.6 Hz, 2 H), 1.48-1.53 (m, 2 H), 1.90- 2.04 (m, 2 H), 2.28-2.46 (m, 2 H), 2.82 (s, 1 H), 2.89-2.90 (m, 1 H), 3.11-3.33 (m, 4 H), 3.49-3.57 (m, 1 H), 5.57 (d, J = 10.0 Hz, 1 H), 5.88-5.93 (m, 1 H); ^{13}C NMR δ d 13.8, 34.6, 41.3, 44.7, 127.5, 129.3; u 19.9, 25.2, 27.0, 28.8, 44.4, 47.7, 171.1, 176.6; IR 2933, 1709, 1625 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_3$: 252.1600, found 252.1606.



2-Cyclopropyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (44). Amino diene **38** (165 mg, 1.20 mmol) and maleic anhydride (148 mg, 1.50 mmol) were dissolved in dichloroethane (3 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue chromatographed to give **44** as an off-white solid (216 mg, 76% yield). R_f = 0.35 (“wet ether”); mp 147-149 °C; ^1H NMR δ 0.48-0.54 (m, 1 H), 0.68-0.88 (m, 3 H), 1.84-1.98 (m, 2 H), 2.26-2.41 (m, 2 H), 2.64-2.70 (m, 1 H), 2.79-2.85 (m, 2H), 3.14-3.21 (m, 3 H), 5.54 (d, J = 8.6 Hz, 1 H), 5.85-5.86 (m, 1 H); ^{13}C NMR δ d 30.3, 34.3, 42.2, 43.6, 127.5, 129.4; u 6.4, 6.9, 24.6, 27.3, 44.4, 173.3, 177.6; IR 3053, 2886, 1708, 1639 cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3$: 236.1287, found 236.1293.

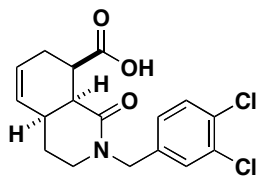


2-Cyclohexyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (45). Amino diene **39** (399 mg, 2.23 mmol) and maleic anhydride (273 mg, 2.78 mmol) were dissolved in dichloroethane (4 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue chromatographed to give **45** as a very light yellow solid (424 mg, 68% yield). R_f = 0.56 ("wet ether"); mp 164.5-168.0 °C; ^1H NMR δ 1.36-1.46 (m, 4 H), 1.58-1.71 (m, 4 H), 1.80- 1.84 (m, 2 H), 1.90-1.95 (m, 2 H), 2.28-2.47 (m, 2 H), 2.78-2.82 (m, 1 H), 2.90-2.95 (m, 1 H), 3.05-3.14 (m, 2 H), 3.21-3.25 (m, 1 H), 4.39-4.46 (m, 1 H), 5.54 (d, J = 10.1 Hz, 1 H), 5.88-5.91 (m, 1 H); ^{13}C NMR δ d 33.9, 41.8, 44.4, 53.6, 127.4, 129.2; u 24.9, 25.4, 25.5, 25.6, 27.0, 29.3, 29.5, 38.3, 170.6, 177.5; IR 2930, 2858, 1708, 1619 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_3$: 278.1756, found 278.1785.



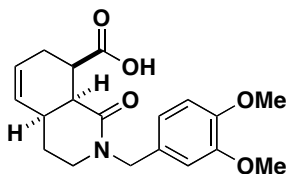
2-Benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (46). Amino diene **40** (187 mg, 1.00 mmol) and maleic anhydride (123 mg, 1.25 mmol) were dissolved in dichloroethane (2.5 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue

chromatographed to give **46** as a very light yellow solid (211 mg, 74% yield). $R_f = 0.56$ ("wet ether"); mp 149.0-152.0 °C; ^1H NMR δ 1.86-1.92 (m, 1 H), 1.95-2.04 (m, 1 H), 2.37-2.51 (m, 2 H), 2.82-2.85 (m, 1 H), 2.88-2.97 (m, 1 H), 3.15-3.19 (m, 2 H), 3.23-3.24 (m, 1 H), 4.53 (d, $J = 14.6$ Hz, 1 H), 4.72 (d, $J = 14.6$ Hz, 1 H), 5.55 (dd, $J = 1.8, 10.0$ Hz, 1 H), 5.88-5.93 (m, 1 H), 7.20 (d, $J = 7.9$ Hz, 2 H), 7.30-7.36 (m, 3 H); ^{13}C NMR δ d 34.8, 41.3, 45.4, 127.5, 127.7, 127.8, 128.7, 129.5; u 25.6, 27.0, 44.0, 51.0, 135.9, 172.0, 175.6; IR 3026, 2923, 1704, 1635 cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3$: 286.1443, found 286.1452.

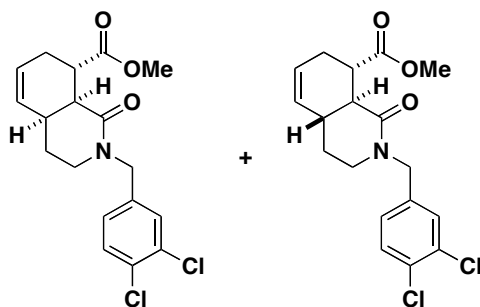


2-(3',4'-Dichlorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (47). Amino diene **41** (256 mg, 1.00 mmol) and maleic anhydride (123 mg, 1.25 mmol) were dissolved in dichloroethane (2.5 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue chromatographed to give **47** as a very light yellow solid (283 mg, 80% yield). $R_f = 0.63$ ("wet ether"); mp 208.0-209.5 °C; ^1H NMR δ 1.89-1.95 (m, 1 H), 2.00-2.09 (m, 1 H), 2.35-2.51 (m, 2 H), 2.86-2.91 (m, 2 H), 3.12-3.22 (m, 2 H), 3.29- 3.31 (m, 1 H), 4.31 (d, $J = 15.0$ Hz, 1 H), 4.79 (d, $J = 15.0$ Hz, 1 H), 5.58 (d, $J = 10.0$ Hz, 1 H), 5.91-5.95 (m, 1 H), 7.05 (dd, $J = 1.7, 8.2$ Hz, 1 H), 7.26 (d, $J = 2.1$ Hz, 1 H), 7.40 (d, $J = 8.2$ Hz, 1 H); ^{13}C NMR δ d 34.7, 41.6, 44.5, 127.1, 127.6, 129.5, 129.7, 130.7; u

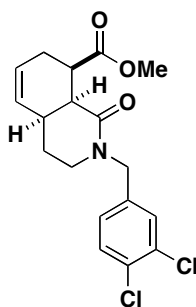
25.2, 27.0, 44.4, 50.6, 131.8, 132.8, 136.4, 171.9, 175.7; IR 3434, 1699, 1626 cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_3$: 354.0664, found 354.0667.



2-(3',4'-Dimethoxybenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic acid (48). Amino diene **42** (349 mg, 1.41 mmol) and maleic anhydride (173 mg, 1.76 mmol) were dissolved in dichloroethane (3.5 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue chromatographed to give **48** as a fluffy white solid (387 mg, 80% yield). R_f = 0.23 ("wet ether"); mp 142.5-144.0 °C; ^1H NMR δ 1.86-1.91 (m, 1 H), 1.96- 2.04 (m, 1 H), 2.40-2.48 (m, 2 H), 2.82-2.86 (m, 1 H), 2.91-2.96 (m, 1 H), 3.13-3.17 (m, 2 H), 3.21-3.24 (m, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 4.35 (d, J = 14.4 Hz, 1 H), 4.76 (d, J = 14.4 Hz, 1 H), 5.54 (d, J = 10.3 Hz, 1 H), 5.85-5.91 (m, 1 H), 6.74-6.76 (m, 2H), 6.80- 6.82 (m, 1 H); ^{13}C NMR δ d 34.5, 41.8, 43.5, 55.8, 55.9, 110.9, 110.9, 120.3, 127.8, 129.0; u 24.7, 26.9, 43.8, 50.6, 128.6, 148.5, 149.2, 171.1, 177.5; IR 2936, 2253, 1706, 1627 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_5$: 346.1654, found 346.1670.



Methyl 2-(3',4'-dichlorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8- carboxylate (49). Amino diene **41** (200 mg, 0.78 mmol) and dimethyl fumarate (150 mg, 1.04 mmol) were dissolved in dichloroethane (3.5 mL) and heated at 165 °C for 1.5 h under microwave irradiation. The solvent was removed in vacuo, and the residue chromatographed to give a colorless oil, **49** as an inseparable 1:1 mixture of diastereomers (262 mg, 91% yield). R_f = 0.84 (5% MeOH in CHCl_3); ^1H NMR δ 1.69 (m, 1H), 1.83 (m, 1H), 2.00 (m, 1H), 2.20 (m, 1H), 2.30-2.33 (m, 1H), 2.42 (m 1H), 2.54-2.61 (m, 1H), 3.14-3.19 (m, 1H), 3.20- 3.24 (m, 1H), 3.30 (m, 1H), 3.58 (m, 1H), 3.72 (s, 3 H), 3.80 (m, 1H); ^{13}C NMR δ 23.5, 27.0, 28.9, 29.8, 30.0, 34.6, 39.4, 40.4, 41.7, 44.6, 45.5, 45.6, 48.8, 49.8, 51.9, 126.0, 126.9, 127.4, 127.5, 128.5, 128.7, 129.3, 129.8, 130.4, 130.6, 131.2, 131.4, 132.5, 132.6, 137.4, 137.4, 170.0, 170.9, 174.7, 176.8; IR 3022, 2945, 2934, 2845, 1734, 1639 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{NO}_3$: 368.0820, found 368.0825.



Methyl 2-(3',4'-dichlorobenzyl)-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8- carboxylate (50). To the carboxylic acid scaffold **49** (67 mg, 0.19 mmol) in MeOH (0.5 mL) and benzene (1.5 mL) was added trimethylsilyldiazomethane solution (0.47 mL, 2 M in ether, 0.945 mmol) and the reaction stirred for 14 h at rt. The solvent was removed in vacuo, and the residue chromatographed to **53** as a colorless oil (69 mg, 98% yield). R_f = 0.09 (25% EtOAc in hexanes); ^1H NMR δ 1.82-1.89 (m, 1 H), 1.99-2.08 (m, 1 H), 2.36-2.39 (m, 1 H), 2.62-2.67 (m, 1 H), 2.86 (m, 1 H), 3.01-3.13 (m, 2 H), 3.42-3.44 (m, 1 H), 3.77 (s, 3 H), 4.15 (d, J = 15.2 Hz, 1 H), 4.83 (d, J = 15.2 Hz, 1 H), 5.55 (dd, J = 0.8, 10.1 Hz, 1 H), 5.87-5.91 (m, 1 H), 6.99 (dd, J = 1.6, 7.9 Hz, 1 H), 7.21 (d, J = 1.2 Hz, 1 H), 7.34 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ d 34.2, 41.0, 42.7, 51.8, 126.9, 127.6, 129.2, 129.3, 130.4; u 23.6, 27.2, 44.1, 49.3, 131.0, 132.4, 137.2, 169.6, 174.1; IR 3509, 3021, 2928, 2250, 1736, 1634 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{NO}_3$: 368.0820, found 368.0825.

Chapter 3: Experimental Details

List of Known Compounds

The following lactams, azidoketones and intermediates are known: 2-(3'-azidopropyl)cyclohexanone (**53**),¹² hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**54**),¹² 2-(3'-azidopropyl)cyclopentanone (**56**),¹² 2-(3'-azidopropyl)-4-*tert*-butylcyclohexanone (**57**),¹² 2-(3'-azidopropyl)cycloheptanone (**60**),¹² ethyl 1-(3'-azidopropyl)-2-oxocyclohexanecarboxylate (**65**),¹² methyl 1-(3'-azidopropyl)-2-oxocyclopentanecarboxylate (**66**),¹² 3-(3'-azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one (**67**),⁶⁴ 2-(3'-azidopropyl)-2,6-dimethylcyclohexanone (**68**),⁶⁵ 2-(3'-azidopropyl)-2-phenylcyclohexanone (**69**),⁶⁶ 6-azidohexan-2-one (**72**),^{12b} methyl 2-hydroxy-3,4-dihydronaphthalene-1-carboxylate (**73**),⁶⁴ 3-(3'-chloropropyl)-3,4-dihydronaphthalen-2(1*H*)-one (**74**),⁶⁴ 2-(3'-chloropropyl)-2,6-dimethylcyclohexanone (**75**),⁶⁵ 2-(3'-chloropropyl)-2-phenylcyclohexanone (**76**),⁶⁶ 4-(2',2'-dimethylhydrazono)-1-propylpiperidine (**78**),⁶⁷ 8-*tert*-butylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**80**),¹² hexahydroindolizin-5(1*H*)-one (**81**),¹² tetrahydro-1*H*-pyrrolizin-3(2*H*)-one (**82**),⁷⁵ 2,3,11,11*a*-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**85**),⁶⁴ and octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (**86**),¹² 2-cyclobutylidene-1,1-dimethylhydrazine,⁶² and 1,1-dimethyl-2-(4-methylcyclohexylidene)hydrazine.⁶³

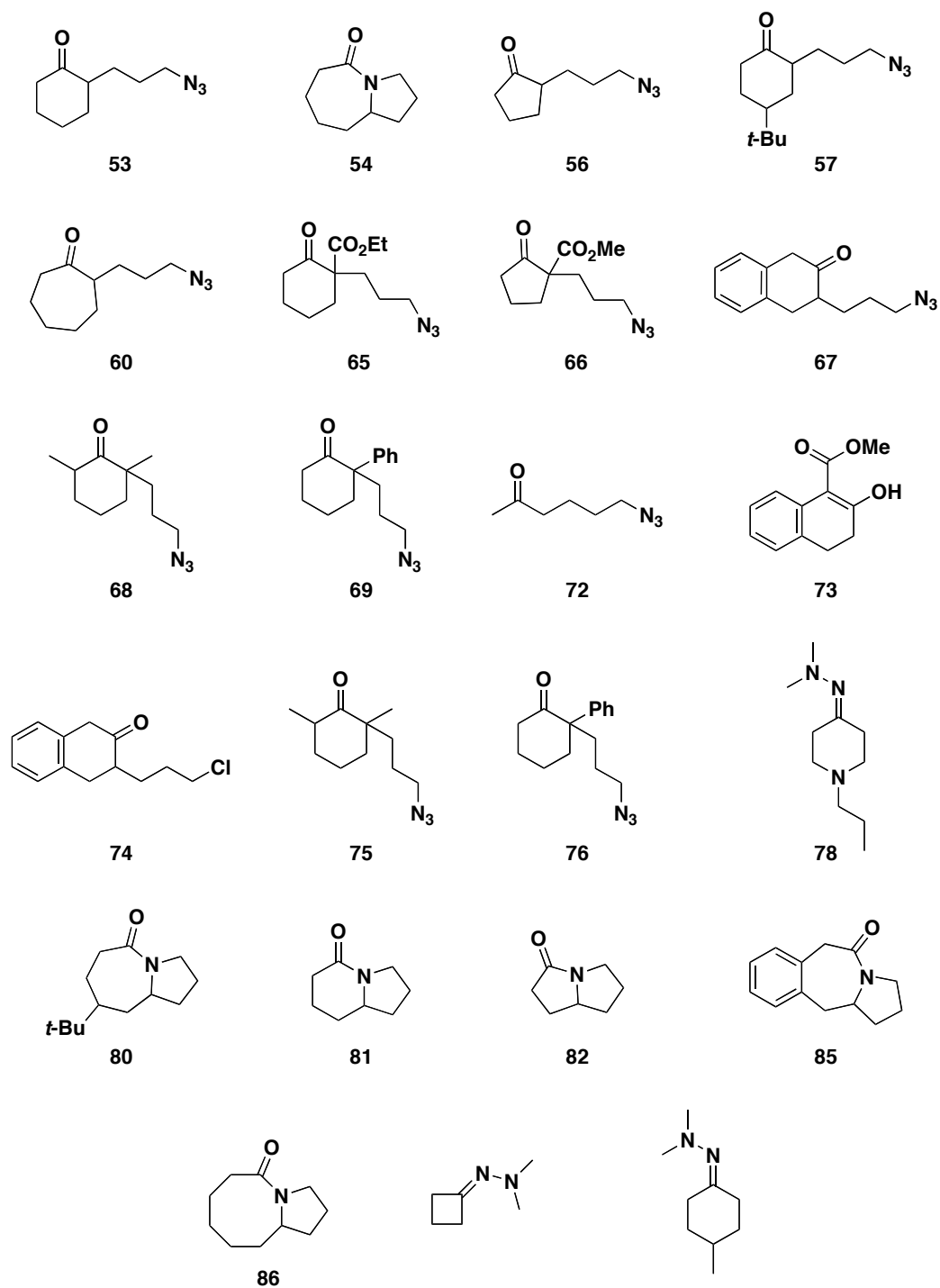
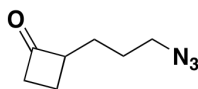
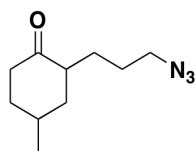


Figure 6. Known lactams, azidoketones and intermediates.

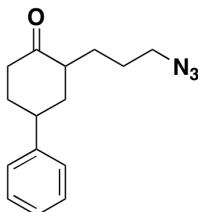


2-(3'-Azidopropyl)-cyclobutanone (55). Compound **55** was synthesized according to literature precedent from Pearson and coworkers.⁷⁶ 2-(3'-Chloropropyl)-cyclobutanone (**63**); see below; (791 mg, 5.40 mmol) afforded the title compound after purification via chromatography (100% hexanes → 10% EtOAc/hexanes) as an oil (720 mg, 87%). ¹H NMR (400.23 MHz) δ 1.59-1.81 (m, 5H), 2.18-2.27 (qd, *J* = 5.2, 10.8 Hz, 1H), 2.89-2.98 (m, 1H), 3.02-3.11 (m, 1H), 3.28-3.31 (t, *J* = 6.40 Hz, 3H). ¹³C NMR (CDCl₃, 100.65 MHz) δ 16.9, 26.5, 26.8, 44.6, 51.1, 59.7, 211.3. IR 1778, 2095, 2928 cm⁻¹. HRMS calcd for C₇H₁₂NO: 126.0919, found 126.0947.



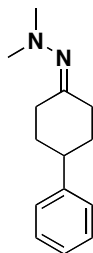
2-(3'-Azidopropyl)-4-methylcyclohexanone (58). Compound **58** was prepared according to literature precedent.¹² 2-(3'-Chloropropyl)-4-methylcyclohexanone (**64**); see below; (868 mg, 4.60 mmol) afforded the title compound, an oil, as an inseparable 2.8:1 mixture of diastereomers (790 mg, 88%). ¹H NMR (CDCl₃, 400 MHz) δ 1.07-1.09 (d, *J* = 6.8 Hz, 3H), 1.11-1.49 (complex, 2H), 1.51-1.64 (m, 3H), 1.69-1.74 (m, 1H), 1.76-1.87 (m, 1H), 1.90-1.99 (m, 1H), 2.04-2.13 (m, 1H), 2.34-2.41 (m, 3H), 3.27-3.30 (m, 2H). ¹³C NMR (CDCl₃, 100.65 MHz) δ 19.8, 26.6, 26.7, 28.0, 34.2, 37.8, 39.8, 47.4, 51.3, 214.1. Minor diastereomer (diagnostic peaks only): 0.98-1.00 (d, *J* = 6.4 Hz, 3H). ¹³C NMR (CDCl₃, 100.65

MHz) δ 21.3, 26.5, 32.1, 35.9, 41.6, 42.4, 49.1, 51.6, 212.7 IR 1711, 2096, 2929, 2951 cm^{-1} . HRMS calcd for $\text{C}_{10}\text{H}_{18}\text{NO}$: 168.1388, found 168.1387.

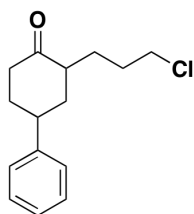


2-(3'-Azidopropyl)-4-phenylcyclohexanone (59). Compound **59** was synthesized according to literature precedent.¹² 2-(3'-Chloropropyl)-4-phenylcyclohexanone **63** see below (1.15 g, 4.60 mmol) afforded the title compound as an oil after purification via chromatography (100% hexanes \rightarrow 10% EtOAc/hexane) as a 4:1 mixture of diastereomers (982 mg, 83%). Preparative TLC was done to separate the diastereomers for characterization (70% CH_2Cl_2 /20% hexanes/10% toluene). HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{ON}$: 230.1546, found 230.1526. IR 1710, 2095, 2933 cm^{-1} . *Trans* diastereomer: R_f = 0.48 (70% CH_2Cl_2 /20% hexanes/10% toluene); ^1H (400.23 MHz) δ 1.60-1.70 (m, 3H), 1.93-1.99 (m, 1H), 2.02-2.16 (m, 2H), 2.17-2.29 (m, 2H), 2.40-2.55 (m, 2H), 2.57-2.67 (m, 1H), 3.17-3.27 (m, 1H), 3.31-3.39 (t, J = 6.4 Hz, 2H), 7.25-7.32 (m, 3H), 7.35-7.40 (m, 2H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 26.7, 28.4, 33.3, 37.4, 38.4, 38.5, 48.8, 51.1, 126.6, 126.7, 128.7, 144.2, 213.7. *Cis* diastereomer: TLC: R_f = 0.49 (70% CH_2Cl_2 /20% hexanes/10% toluene); ^1H (400.23 MHz) δ 1.35-1.39 (m, 1H), 1.60-1.75 (m, 3H), 1.88-2.02 (m, 2H), 2.25-2.34 (m, 2H), 2.50-2.59 (m, 3H), 3.11-3.20 (m, 1H), 3.25-

3.36 (m, 2H), 7.24-7.27(m, 3H), 7.33-7.38 (m, 2H). ^{13}C NMR (CDCl_3 , 100.65 MHz) δ 26.4, 26.5, 35.0, 41.5, 41.9, 43.5, 49.6, 51.6, 126.7, 126.7, 128.6, 144.5, 211.7.

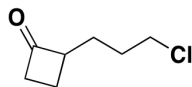


1,1-Dimethyl-2-(4'-phenylcyclohexylidene)hydrazine (61). Compound **61** was prepared according to literature precedent.¹² 4-Phenylcyclohexanone (10.0 g, 57.4 mmol) was dissolved in 80 mL of benzene and to this mixture was added *N,N*-dimethyl hydrazine (6.90 g, 115 mmol) followed by *p*-toluenesulfonic acid (0.55 g, 2.87 mmol). The flask was then equipped with a Dean–Stark trap and a reflux condensor, and the mixture was heated to reflux overnight. The reaction mixture was then concentrated to afford a solid that was recrystallized from hexanes/EtOAc to give 11.5 g (92%) of the hydrazone as a white solid, mp 56–58 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.62-1.82 (m, 2H), 1.94-2.03 (td, J = 5.2, 13.6 Hz, 1H), 2.07-2.14 (m, 2H), 2.31-2.39 (m, 1H), 2.51 (s, 6H), 2.54-2.60 (m, 1H), 2.80-2.89 (m, 1H), 3.40-3.47 (m, 1H), 7.23-7.25 (m, 3H), 7.29-7.33 (m, 2H). ^{13}C NMR (100.65 MHz, CDCl_3) δ 28.2, 33.8, 34.4, 35.7, 43.8, 126.3, 126.7, 128.5, 145.8, 169.0; IR 700, 1716, 2928 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2$: 217.1705, found 217.1706.



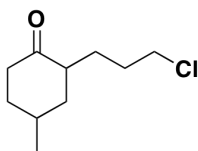
2-(3'-Chloropropyl)-4-phenylcyclohexanone (62). To a dried flask was added diisopropylamine (1.08 g, 10.6 mmol) and 13 mL of THF. This mixture was cooled to 0 °C, and *n*-butyllithium (2.5 M, 10.1 mmol) was added. The reaction was allowed to stir for approximately 20-30 min, and 1,1-dimethyl-2-(4-phenylcyclohexylidene)hydrazine (**61**); (2.00 g, 9.25 mmol) in a small amount of THF was added dropwise over 1-2 min. This mixture was allowed to stir for ca. 1–1.5 h at 0 °C. Then 1-chloro-3-iodopropane (2.46 g, 12.0 mmol) was added and the stirred mixture was warmed to rt over 4 h. The reaction was monitored by TLC and upon completion was poured into a biphasic mixture of 2N H₂SO₄ (32 mL) and diethyl ether (195 mL) and stirred vigorously for 15-20 min. The organic layer was separated and the aqueous layer was washed with diethyl ether (2 × 50 mL). The combined organic layers were then washed with brine (1 × 75 mL) and dried with Na₂SO₄. The dried organic layer was filtered and concentrated to give an oil. The crude product was purified by silica chromatography (100% hexanes → 5% ethyl acetate/ hexane) to give 2-(3'-chloropropyl)-4-phenylcyclohexanone as a mixture of diastereomers in 1.9 g (82%). The diastereomers could be separated for characterization using preparative TLC (80% CH₂Cl₂/20% hexanes). *Trans* diastereomer: *R_f* = 0.48 (80% CH₂Cl₂/20% hexanes). ¹H NMR (CDCl₃, 400 MHz) δ 1.68-1.81 (complex, 3H), 1.91-2.06 (complex, 3H), 2.11-2.20 (m, 2H), 2.33-2.39 (m, 1H), 2.44 (m, 1H), 2.59-2.78

(m, 1H), 3.20-3.24 (m, 1H), 3.57-3.61 (m, 2H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 28.6, 30.2, 33.3, 37.4, 38.4, 38.6, 44.7, 48.6, 126.6, 126.8, 128.7, 144.3, 213.7. *Cis* diastereomer: $R_f = 0.49$ (80% CH_2Cl_2 /20% hexanes). ^1H NMR (CDCl_3 , 400 MHz) δ 1.38-1.49 (m, 1H), 1.65-1.72 (m, 1H), 1.77-1.98 (complex, 4H), 2.25-2.36 (m, 2H), 2.50-2.63 (m, 3H), 3.11-3.20 (m, 1H), 3.52-3.61 (m, 2H), 7.24-7.29 (m, 3H), 7.33-7.38 (m, 2H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 26.7, 30.3, 35.0, 41.4, 41.9, 43.5, 45.1, 49.4, 126.7, 126.7, 144.5, 211.7. IR 1710, 2932 cm^{-1} . HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{OCl}$: 251.1203, found 251.1204.



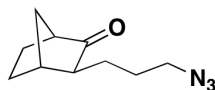
2-(3'-Chloropropyl)-cyclobutanone (63). To a dried flask was added dry THF (20 mL), cyclobutanone *N,N*-dimethylhydrazone⁶² (1.12 g, 10.0 mmol). The reaction was cooled to $-5\text{ }^{\circ}\text{C}$ and *n*-butyllithium (2.5M in hexanes, 10.5 mmol) was added dropwise via syringe. This mixture was stirred for 1–2 h at this temperature at which time 1-chloro-3-iodopropane (2.25 g, 11.0 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was quenched with the addition of 2N HCl (20 mL). After vigorous stirring for ca. 30 min the mixture was extracted with diethyl ether ($4 \times 30\text{ mL}$). The combined organic layers were washed sequentially with water ($1 \times 25\text{ mL}$) and brine ($1 \times 30\text{ mL}$), and dried over Na_2SO_4 . Filtration and concentration provided an oil which was purified using silica chromatography (100% hexanes \rightarrow 7% EtOAc/hexanes) to afford **63** (820

mg, 56%). ^1H NMR (CDCl_3 , 400 MHz) δ 1.67-1.74 (m, 2H), 1.81-1.94 (m, 3H), 2.19-2.29 qd, $J = 5.2, 10.4$ Hz, 1H), 2.94-3.00 (m, 1H), 3.03-3.14 (m, 1H), 3.30-3.35 (m, 1H), 3.54-3.58 (m, 2H); ^{13}C NMR (CDCl_3 , 100.57 MHz) δ 16.9, 26.9, 30.1, 44.5, 44.6, 59.6, 211.3. IR 1777, 2926, 2958 cm^{-1} . HRMS calcd for $\text{C}_7\text{H}_{11}\text{OCl}$: 146.0498, found 146.0493.



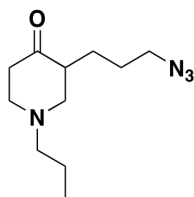
2-(3'-Chloropropyl)-4-methylcyclohexanone (64). To a dried flask was added diisopropylamine (1.52 g, 15.0 mmol) and 20 mL of THF. This mixture was cooled to 0 °C, and *n*-butyllithium (2.5 M, 14.3 mmol) was added. The reaction was allowed to stir for approximately 20-30 min, and 1,1-dimethyl-2-(4'-methylcyclohexylidene)hydrazine⁷⁴ (2.10 g, 13.6 mmol) in a small amount of THF was added dropwise over 1-2 min. This mixture was allowed to stir for ca. 1-1.5 h at 0 °C. Then 1-chloro-3-iodopropane (3.48 g, 17.0 mmol) was added and the stirred mixture was warmed to rt over 4 h. The reaction was monitored by TLC and upon completion was poured into a biphasic mixture of 2N H_2SO_4 (48 mL) and diethyl ether (290 mL) and stirred vigorously for 15-20 min. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 \times 50 mL). The combined organic layers were then washed with brine (1 \times 75 mL) and dried with Na_2SO_4 . The dried organic layer was filtered and concentrated to give an oil. The crude product

was purified by silica chromatography (100% hexanes \rightarrow 5% ethyl acetate/ hexane) to give the title compound as an inseparable ca. 2:1 mixture of diastereomers (2.15 g, 84%). Major diastereomer: ^1H NMR (CDCl_3 , 400 MHz) δ 1.01 (d, $J = 6.6$ Hz, 3H), 1.29-1.41 (m, 1H), 1.50-1.62 (m, 1H), 1.73-2.15 (complex, 7H), 2.32-2.47 (m, 3H), 3.50-3.61 (m, 2H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 21.3, 26.8, 30.4, 32.1, 36.0, 41.6, 42.4, 45.2, 49.0, 212.7. Minor diastereomer: (diagnostic peaks only): ^1H NMR (CDCl_3 , 400 MHz) δ 1.09 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 19.9, 26.6, 28.2, 30.3, 34.3, 37.9, 39.9, 44.9, 47.4, 214.3. IR 1709, 2927, 2950 cm^{-1} . HRMS not found using ES, EI, CI, or FAB $^+$.

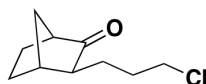


(1*S,3*S**,4*R**)-3-(3'-Azidopropyl)bicyclo[2.2.1]heptan-2-one (70).**

Compound **70** was prepared according to literature precedent.¹² (1*S**,3*S**,4*R**)-3-(3'-chloropropyl)bicyclo[2.2.1]heptan-2-one (**76**) see below (860 mg, 4.60 mmol) afforded the title compound after silica chromatography (100% hexanes \rightarrow 10% EtOAc/hexanes) as an oil (780 mg, 88%). ^1H NMR (400.23 MHz) δ 1.38-1.61 (m, 5H), 1.71-1.76 (m, 3H), 1.82-1.87 (m, 3H), 2.41-2.43 (m, 1H), 2.55-2.56 (m, 1H), 3.26-3.36 (m, 2H). ^{13}C NMR (CDCl_3 , 100.65 MHz) δ 24.0, 26.4, 27.6, 28.0, 34.8, 39.5, 49.5, 51.2, 53.3, 219.6. IR 1741, 2097, 2877, 2956 cm^{-1} . HRMS calcd for $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O}$: 194.1293, found 194.1161.



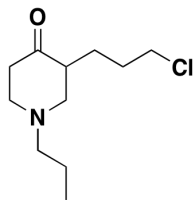
2-(3'-Azidopropyl)-1-propylpiperidin-4-one (72). Compound **72** was prepared according to literature precedent.¹² 2-(3'-Chloropropyl)-1-propylpiperidin-4-one (**79**) (1.00 g, 4.60 mmol) afforded the title compound after silica chromatography (5% → 15% EtOAc/hexanes) as an oil (870 mg, 84%). ¹H NMR (400.23 MHz) δ 0.91 (t, *J* = 7.6 Hz, 3H), 1.35-1.38 (m, 1H), 1.49-1.54 (m, 2H), 1.71-1.87 (m, 3H), 2.14 (t, *J* = 10.8 Hz, 1H), 2.30-2.42 (m, 4H), 2.46-2.60 (m, 2H), 3.02-3.06 (m, 2H), 3.46-3.56 (m, 2H). ¹³C NMR (CDCl₃, 100.65 MHz) δ 11.9, 20.6, 24.8, 30.3, 41.0, 44.9, 49.0, 53.8, 59.2, 59.3, 210.4. IR 1714, 2096, 2806, 2959 cm⁻¹. HRMS not found with ES, CI, or FAB⁺.



(1*S,3*S**,4*R**)-3-(3'-Chloropropyl)bicyclo[2.2.1]heptan-2-one (77).**

Compound **77** was prepared according to literature precedent.⁵⁹ Norcamphor (2.50 g, 22.7 mmol) and 1-chloro-3-iodopropane (7.89 g, 38.6 mmol) afforded the title compound after silica chromatography (100% hexanes → 7% EtOAc/hexanes) as an oil (3.16 g, 75%). ¹H NMR (CDCl₃, 400.23 MHz) δ 1.4-1.53 (m, 4H), 1.62-1.72 (m, 2H), 1.82-1.93 (m, 5H), 2.41-2.43 (m, 1H), 2.55-2.56 (m, 1H), 3.51-3.59 (m, 2H), 3.51-3.59 (m, 2H). ¹³C NMR (CDCl₃, 100.62 MHz) δ 24.0, 26.6, 27.9, 31.1, 34.8,

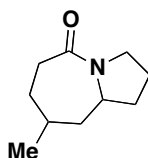
39.6, 44.7, 49.5, 53.0, 219.6. IR 1742, 2958 cm^{-1} . HRMS calcd for $\text{C}_{10}\text{H}_{15}\text{OCl}$: 186.0811, found 186.0796.



3-(3'-Chloropropyl)-1-propylpiperidin-4-one (79). To a dried flask was added 20 mL of THF and 1-propylpiperidin-4-one dimethylhydrazone (**78**);⁶⁷ (2.00 g, 9.19 mmol). This mixture was cooled to 0 °C, and *n*-butyllithium (2.5 M, 10.1 mmol) was added. After stirring for ca. 1h, 1-chloro-3-iodopropane (2.25 g, 11.03 mmol) in a small amount of THF was added, and the stirred mixture was warmed to rt over 16 h. At this time, the reaction mixture was poured into ice cold 2M HCl (23.2 mL) and was stirred vigorously for ca. 30 minutes. The organic phase was then separated and the aqueous phase extracted with CH_2Cl_2 (4 \times 30 mL). The combined organic extracts were then washed sequentially with saturated aqueous NaHCO_3 solution (2 \times 25 mL), water (1 \times 20 mL), and brine (1 \times 30 mL), and then dried (Na_2SO_4). Filtration and concentration afforded the title compound after silica chromatography (5% EtOAc/hexanes \rightarrow 20% EtOAc/hexanes) as an oil (1.54 g, 77%). ^1H NMR (400.23 MHz) δ 0.93 (t, J = 7.2 Hz, 3H), 1.38-1.41 (m, 1H), 1.49-1.59 (m, 2H), 1.73-1.95 (m, 3H), 2.13-2.19 (m, 1H), 2.34-2.45 (m, 4H), 2.48-2.62 (m, 2H), 3.02-3.10 (m, 2H), 3.49-3.56 (m, 2H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 11.9, 20.6, 24.9, 30.3, 41.1, 44.9, 49.3, 53.8, 59.2, 59.3, 210.4. IR 1716, 2959 cm^{-1} . HRMS calcd for

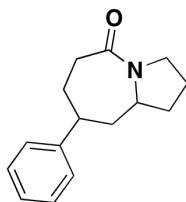
C₁₁H₂₁NOCl: 218.1313, found 218.1289.

General procedure for the catalytic Schmidt reaction to yield 8-methylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (83).

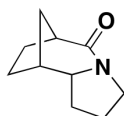


To a clean 0.5-2 mL microwave vial equipped for stirring was added 2-(3'-azidopropyl)-4-methylcyclohexanone (**58**), (79 mg, 0.41 mmol), and 0.75 mL of distilled water. To this mixture was added 25 mol% Sc(OTf)₃ (0.101 mmol, 49.8 mg) followed by 10 mol% of a 40% solution of *n*-Bu₄OH in water (0.041 mmol, 26.3 mg) and another 0.75 mL of distilled water. The vial was capped, and irradiated in the microwave for 4 h at 180 °C. The reaction mixture was diluted with 1 mL of water and extracted with CH₂Cl₂ (6 × 7 mL). The combined organic extracts were washed with brine (2 × 7 mL) and dried over Na₂SO₄. The dried organic layer was filtered and concentrated to provide a brown oil. Silica chromatography of the resulting oil eluted with a gradient of 10% EtOAc/hexanes → 100% EtOAc afforded the title compound as an inseparable 3:1 mixture of diastereomers (40 mg, 59%). Major diastereomer: ¹H NMR (CDCl₃, 400.23) δ 0.94 (d, *J* = 6.4 Hz, 3H), 1.09-1.29 (m, 2H), 1.52-1.89 (complex, 5H), 2.05-2.35 (complex, 2H), 2.40-2.64 (complex, 2H), 3.33-3.44 (m, 1H), 3.61-3.89 (complex, 2H). ¹³C NMR (CDCl₃, 100.65 MHz) δ 23.1,

23.2, 31.4, 34.9, 36.3, 37.1, 44.1, 46.7, 57.8, 173.7. Minor diastereomer (diagnostic peaks only): ^1H NMR (CDCl_3 , 400.23) δ 1.05 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100.65 MHz) δ 18.3, 23.3, 28.8, 28.9, 32.2, 34.8, 40.9, 52.7. IR 1626, 2868, 2918, 2956 cm^{-1} . HRMS calcd for $\text{C}_{10}\text{H}_{18}\text{NO}$: 168.1388, found 168.1379.



8-Phenylhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (84). Compound **84** was prepared according to the general procedure described for **83**. 2-(3'-Azidopropyl)-4-phenylcyclohexanone (**59**), (104 mg, 0.41 mmol) afforded the title compound, an oil, as an inseparable 4:1 mixture of diastereomers (51 mg, 55%). Major diastereomer: ^1H NMR (400.23 MHz) δ 1.67-2.10 (complex, 7H), 2.11-2.33 (complex, 1H), 2.50-2.86 (complex, 3H), 3.44-3.65 (complex, 1H), 3.70-3.80 (m, 1H), 3.81-4.05 (complex, 1H), 7.17-7.38 (complex, 5H). ^{13}C NMR (CDCl_3 , 100.57 MHz) δ 23.5, 30.6, 34.9, 37.5, 43.6, 46.9, 48.1, 58.0, 126.5, 126.6, 128.6, 146.4, 173.5. Minor diastereomer (diagnostic peaks only): ^1H NMR (CDCl_3 , 400.23) δ 3.97-4.09 (m, 1H). ^{13}C NMR (CDCl_3 , 100.62 MHz) δ 22.9, 27.4, 34.0, 34.5, 39.3, 39.4, 46.6, 54.6, 126.3, 127.2, 144.5, 172.2. IR 1632, 2868, 2923, 3473 cm^{-1} . HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{NO}$: 230.1545, found 230.1525.



(1*R, 7*S**, 10*aR**)-Octahydro-7,10-methanopyrrolo[1,2-*a*]azepin-6(2*H*)-one (87).**

To a dried flask containing (1*S**,3*S**,4*R**)-3-(3'-azidopropyl)bicyclo[2.2.1]heptan-2-one (**70**), (0.05 g, 0.26 mmol) was added trifluoroacetic acid (2.5 mL). This mixture was capped and heated to reflux overnight. The reaction was cooled to rt, concentrated and diethyl ether (40 mL) was then added. The organic layer was washed sequentially with saturated NaHCO₃ solution, brine and then dried over Na₂SO₄ to give afford an oil. Purification via silica chromatography (100% EtOAc) provided the title compound (14 mg, 33%). *R_f* = 0.45 (100% EtOAc). ¹H NMR (CDCl₃, 400.23) δ 1.38-1.43 (complex, 1H), 1.48-1.53 (dt, *J* = 4.4, 11.8 Hz, 1H), 1.70-1.93 (complex, 8H), 2.46 (m, 1H), 2.77 (m, 1H), 3.04-3.09 (m, 1H), 3.12-3.16 (m, 1H), 3.83-3.90 (m, 1H). ¹³C NMR (CDCl₃, 100.65 MHz) δ 21.8, 28.3, 29.4, 30.3, 31.9, 36.2, 42.9, 43.5, 65.5, 175.1. IR 1641, 2956, 3428 cm⁻¹. HRMS calcd for C₁₀H₁₅NO: 166.1232, found 166.1243.

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